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伏帶疹®活性帶狀疱疹疫苗

ZOSTAVAX® [zoster virus vaccine live (Oka/Merck)]

冷藏安定配方

Refrigerator-stable formulation

衛署菌疫輸字第 000873 號

本藥須由醫師處方使用

說　明

ZOSTAVAX*為一內含活性減毒 Oka/Merck 株水痘帶狀疱疹病毒(varicella-zoster virus；VZV)的冷凍乾燥製劑。此病毒最初是在自然發生水痘的兒童身上取得，然後導入人類胚胎肺細胞培養，再使其在天竺鼠胚胎細胞培養以馴化繁殖，最後再於人類雙套染色體細胞培養(WI-38)中繁殖。這些病毒會在默克研究實驗室(Merck Research Laboratories；MRL)的不含任何外來異物的人類雙套染色體細胞培養基(MRC-5)中進行進一步的繼代培養。本活性減毒帶狀疱疹疫苗是一種含有蔗糖、磷酸鹽、麩胺酸鹽、並以明膠做為安定劑進行處理的冷凍乾燥製劑。

依指示泡製後的 ZOSTAVAX 為一無菌皮下注射劑。完成泡製並於室溫下存放達 30 分鐘的情況下，每劑 0.65 毫升的疫苗中含有至少 19,400 個 PFU(plaque-forming units;斑點形成單位)的 Oka/Merck 株水痘帶狀疱疹病毒(VZV)。

每劑 0.65 毫升的疫苗中也含有：41.05 毫克的蔗糖、20.53 毫克的水解豬皮明膠、8.55 毫克的尿素、5.25 毫克的氯化鈉、0.82 毫克的 L-麩胺酸鈉、0.75 毫克的磷酸氫二鈉、0.13 毫克的磷酸二氫鉀、0.13 毫克的氯化鉀；MRC-5 細胞的殘留成分，包括 DNA 與蛋白質；以及微量的 neomycin 與小牛血清。本品不含任何防腐劑。

臨床藥理學

帶狀疱疹

帶狀疱疹(Herpes zoster; HZ)(俗稱皮蛇)是水痘帶狀疱疹病毒(VZV)再度活化的表現，這種病毒在初次感染時會引發水痘。初次感染之後，此病毒會潛伏在背根神經節或腦感覺神經節中，直到再度活化引發帶狀疱疹。帶狀疱疹的一般特徵為延著皮節分佈的單側性、疼痛性、水泡性皮疹。

雖然水泡性皮疹是帶狀疱疹最明顯的表徵，但最常見的耗弱性症狀是疼痛；疼痛症狀可能會發生於感染的前驅期、急性發疹期、以及疱疹後期。曾有報告指出，在急性發疹期間，免疫功能正常的人高達 90%會發生局部疼痛。

任何曾經感染水痘帶狀疱疹病毒(VZV)的人，包括無水痘臨床病史的人，都有發生帶狀疱疹的危險，一般認為這是因為對水痘帶狀疱疹病毒(VZV)免疫力衰退的緣故。在美國，幾乎所有的成人(~98%)對帶狀疱疹都具有感受性，且每年估計會發生 1 百萬個病例。由於人口平均年齡不斷提高，相信這個數字還會繼續攀升。帶狀疱疹的發生率與嚴重度，以及其併發症的發生頻率與嚴重度，都會隨年齡而明顯升高，並有三分之二的病例是發生於 50 歲以上的人。最近的研究顯示，一般大眾一生中發生帶狀疱疹的終生風險估計可高達 30%。據估計，在 85 歲之前將會有 50%的人曾經發生帶狀疱疹。

因帶狀疱疹而住院治療的病例有 70%至 80%都是發生於免疫功能正常的人。在美國，每年會發生約 50,000 至 60,000 個和帶狀疱疹有關的住院病例，包括 12,000 至 19,000 個初步診斷為帶狀疱疹的病例。

帶狀疱疹可能會引發嚴重的併發症，如帶狀疱疹後神經痛(Postherpetic Neuralgia; PHN)、留下疤痕、細菌性繼發感染、運動神經麻痺、肺炎、腦炎、Ramsay Hunt 症候群、視覺損害、聽力喪失、以及死亡。

帶狀疱疹所引起的疼痛與不適可能會持續一段時間，並會造成失能，這會使生活品質及行為能力降低至和充血性心臟衰竭、心肌梗塞、第 II 型糖尿病及重鬱症等耗弱性疾病相當的程度。

帶狀疱疹後神經痛

在免疫功能正常的宿主中，帶狀疱疹後神經痛(PHN)是最常見的嚴重併發症，也是引發帶狀疱疹相關疾病的主因。根據已發表之文獻中的估計，PHN 在美國人口中的盛行率為 500,000 至 1,000,000 例。PHN 的發生頻率與嚴重度會隨年齡而升高，在 50 歲以上的患者中，有 25%至 50%的帶狀疱疹病例可能會因併發 PHN 而更加惡化。PHN 的特徵包括觸痛、灼熱感、抽痛、刺痛、劇痛、以及(或)急劇的疼痛，可能會持續數月甚或數年之久，也可能會導致情緒上的痛苦。在併發 PHN 的患者中，至少 90%會出現觸痛的症狀(由非疼痛性刺激所引起的疼痛)，這是最令人苦惱及最具耗弱性的疼痛類型之一。有數種不同的 PHN 定義已廣為醫界所採用，包括在皮疹發生後持續超過 90 天以上的疼痛。

作用機轉

發生帶狀疱疹的風險似乎和水痘帶狀疱疹病毒(VZV)特異性免疫力的衰退有因果上的關聯性。ZOSTAVAX 已證實可提高水痘帶狀疱疹病毒(VZV)特異性免疫力，一般也認為這就是此疫苗據以預防帶狀疱疹及其併發症的作用機轉(參見*免疫生成性*)。

臨床研究

ZOSTAVAX 之臨床預防效果的評估

ZOSTAVAX 針對 50 至 59 歲受試者所做的療效及安全性研究（ZEST）

ZOSTAVAX 療效及安全性研究（ZEST）為一項安慰劑對照性的雙盲臨床試驗，該研究共有 22,439 位 50-59 歲的受試者於隨機分組後分別接種一劑 ZOSTAVAX（11,211 人）或安慰劑（11,228 人），並接受中位數 1.3 年（0 至 2 年）的追蹤以觀察帶狀疱疹的發生情形。所有的帶狀疱疹疑似病例都由一個臨床評估委員會進行判定。帶狀疱疹病例必須經由 PCR 確認（86%），或在病毒沒有被偵測到的情況下，則由臨床評估委員會來判定（14%）。

相較於安慰劑，ZOSTAVAX 能有效降低帶狀疱疹的發生率（ZOSTAVAX 組為 30 例 [2.0 /1000 人年] vs 安慰劑組為 99 例 [6.6 /1000 人年]；p<0.001）。ZOSTAVAX 對帶狀疱疹的預防效果為 69.8%（95% CI：[54.1 至 80.6%]）。

*針對 60 歲（含）以上受試者所進行的帶狀疱疹預防研究(Shingles Prevention Study; SPS)*帶狀疱疹預防研究(Shingles Prevention Study; SPS)是一項針對 ZOSTAVAX 所進行的安慰劑對照性雙盲臨床試驗；在這項研究中，共有 38,546 位 60 歲(含)以上的受試者於隨機分組後分別接種一劑的 ZOSTAVAX (n=19,270)或安慰劑(n=19,276)，並接受平均 3.1 年(1 天至 4.90 年)的追蹤，藉以觀察其發生帶狀疱疹的情形。隨機分組時並依年齡分成 60-69 歲組與≥70 歲組。所有的帶狀疱疹疑似病例都由一個臨床評估委員會進行判定。帶狀疱疹病例的確認依據依序為 PCR、局部病灶培養、或是臨床評估委員會的判定。在兩個接種組(ZOSTAVAX 組與安慰劑組)中，發生帶狀疱疹的受試者都接受 famciclovir 的治療，並於必要時給予止痛藥物。疼痛嚴重度的評估依據為利用帶狀疱疹簡式疼痛問卷(Zoster Brief Pain Inventory; ZBPI，一種已獲確認的問卷)進行評估，在 0 至 10 分量表上所呈現的「最嚴重疼痛」評分。評分如為 3 (含)以上即視為具有臨床意義，因為已經會對日常活動(activities of daily living; ADL)造成明顯的干擾。

和安慰劑相比較，ZOSTAVAX 可明顯降低發生帶狀疱疹及 PHN 的風險。此外，HZ 疼痛症狀疾病負擔(burden of illness; BOI)分數的評估結果也顯示，ZOSTAVAX 可明顯減輕急性與慢性帶狀疱疹相關疼痛。(參見表 1)

表 1

在帶狀疱疹預防研究中

ZOSTAVAX 和安慰劑的預防效果之比較

疫苗

終點評估指標	預防效果	95% CI
帶狀疱疹的發生率	51%	44至58%
PHN*的發生率	67%	48至79%
HZ疼痛症狀疾病負擔(BOI)**	61%	51至69%

* 在皮疹發生後，持續時間或出現時間超過 90 天以上且具臨床意義的帶狀疱疹相關疼痛。

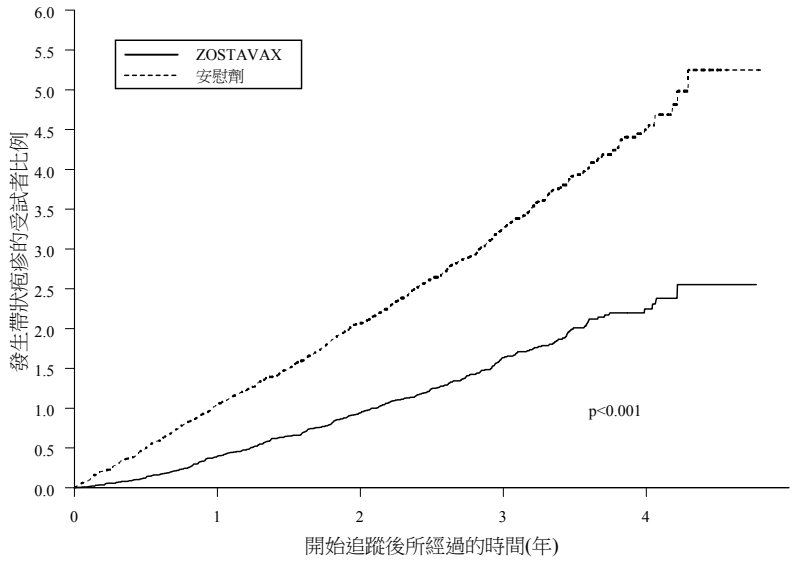
** HZ 疼痛症狀疾病負擔(BOI)分數是一種涵蓋急性與慢性帶狀疱疹相關疼痛症狀在 6 個月追蹤期間之發生率、嚴重度及持續時間的綜合評分。

和安慰劑相比較，ZOSTAVAX 可明顯降低帶狀疱疹的發生率(315 例[5.4 /1000 人年]；安慰劑組則為 642 例[11.1 /1000 人年]；p<0.001)。ZOSTAVAX 對帶狀疱疹的預防效果為 51% (95% CI：[44 至 58%])。ZOSTAVAX 可使 60-69 歲與 70-79 歲之年齡層中的帶狀疱疹發生率分別降低 64% (95% CI：[56 至 71%])與 41% (95% CI：[28 至 52%])。疫苗接種者中的帶狀疱疹隨時間累計之發生率也有明顯降低的現象(p<0.001；圖 1)。

圖 1

帶狀疱疹預防研究中的

帶狀疱疹隨時間*累計之發生率的 Kaplan-Meier 標繪圖



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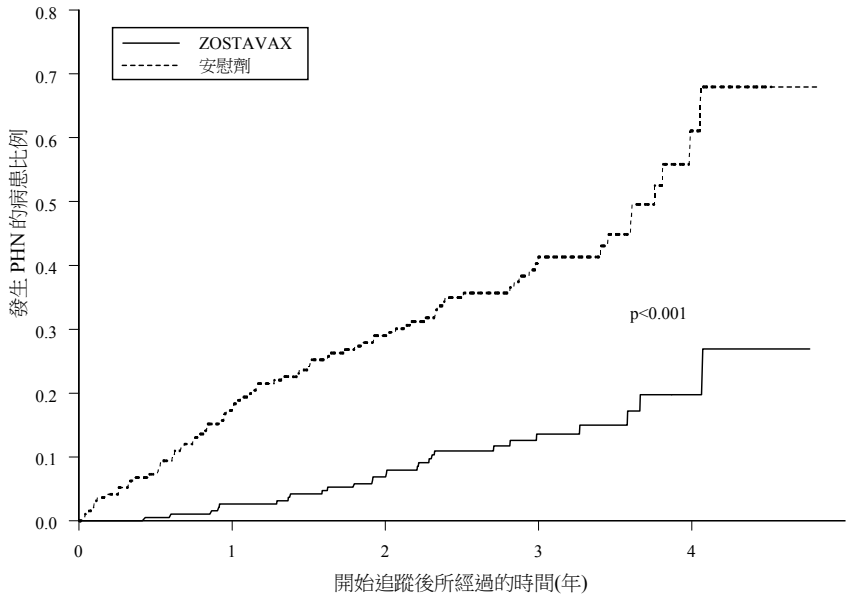
*有少數受試者在第 4 年之後仍繼續接受追蹤。

和安慰劑相比較，ZOSTAVAX 可降低 PHN 的發生率(27 例[0.5/1000 人年]，安慰劑組則為 80 例[1.4/1000 人年]；p<0.001)。在這項試驗中，PHN 的定義為在皮疹發生後，持續時間或出現時間超過 90 天以上且具臨床意義的帶狀疱疹相關疼痛。ZOSTAVAX 對 PHN 的預防效果為 67% (95% CI：[48 至 79%])，且兩個年齡層中(60-69 歲與≥ 70 歲)的降低程度大致相當。此外，當採用不同的疼痛持續時間截點(30、60、120 或 182 天)來定義 PHN 時，ZOSTAVAX 的預防效果亦無明顯變化。和安慰劑相比較，ZOSTAVAX 可明顯降低 PHN 的隨時間累計的發生率(p<0.001；圖 2)。

圖 2

帶狀疱疹預防研究中的

PHN 隨時間*累計發生率 Kaplan-Meier 標繪圖



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*少數受試者在第 4 年之後仍繼續接受追蹤。

ZOSTAVAX 對於預防接種後仍發生帶狀疱疹的患者產生 PHN 的預防效果，即除了預防帶狀疱疹發生外的 PHN 預防效果為 39% (95% CI：[7 至 59%])。在 70-79 歲之年齡層中，該預防效果為 55% (95% CI：[18 至 76%])，具有相對統計顯著性。

和安慰劑相比較，ZOSTAVAX 可使 HZ 疼痛症狀疾病負擔(BOI)分數降低約 61% (95% CI：[51 至 69%])。ZOSTAVAX 在兩個年齡層中(60-69 歲與≥ 70 歲)使 HZ 疼痛症狀疾病負擔(BOI)分數降低的程度大致相當。HZ 疼痛症狀疾病負擔(BOI)分數是一種涵蓋急性與慢性帶狀疱疹相關疼痛症狀在 6 個月追蹤期間之發生率、嚴重度及持續時間的綜合評分。

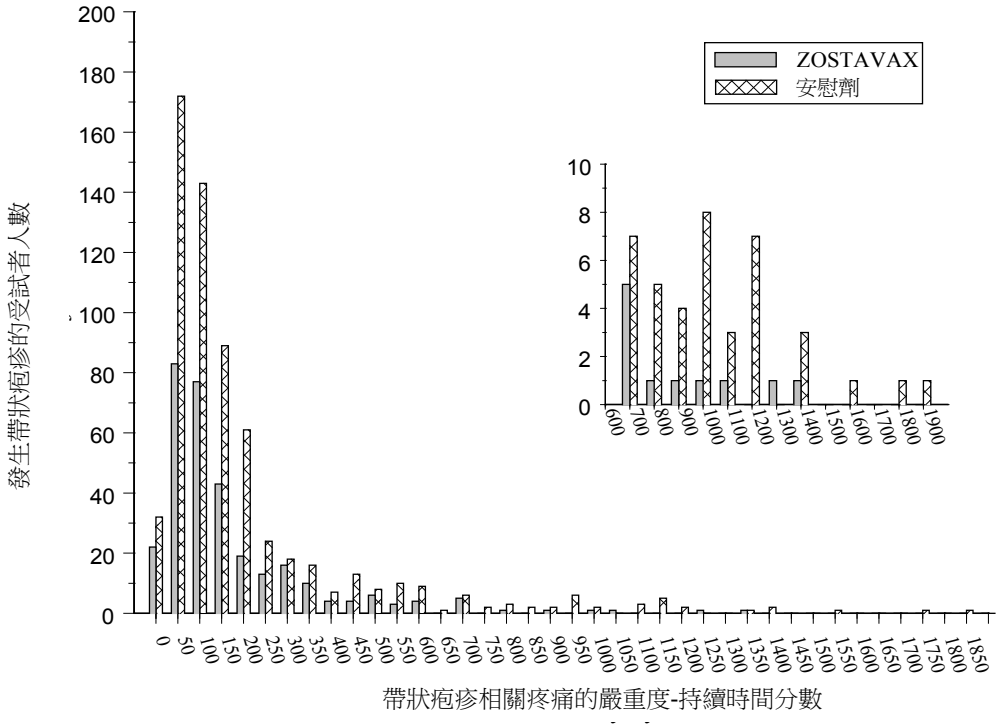
和安慰劑相比較，ZOSTAVAX 可使嚴重且持續時間較長之帶狀疱疹相關疼痛(嚴重度-持續時間分數>600)的發生率降低 73% (95% CI：[46 至 87%])。在接種 ZOSTAVAX 的受試者中，嚴重度-持續時間分數>600 者有 11 位，在接種安慰劑的受試者中則有 40 位。(參見圖 3)

在發生帶狀疱疹的接種者中，和安慰劑相比較，ZOSTAVAX 可使帶狀疱疹相關疼痛明顯減輕。在 6 個月追蹤期間，嚴重度-持續時間分數降低了 22% (ZOSTAVAX 組的平均分數為 141，安慰劑組則為 181；p=0.008)。

圖 3

在帶狀疱疹預防研究中

帶狀疱疹相關疼痛的隨時間嚴重度-持續時間分數*



*此圖所示為嚴重度-持續時間分數>600 的受試者人數。例如，每日最嚴重疼痛的評估結果為最高分 10 分，且持續>60 天，則其嚴重度-持續時間分數即為>600。

在發生 PHN 的接種者中，和安慰劑相比較，ZOSTAVAX 可使 PHN 相關疼痛明顯減輕。在皮疹發生後 90 天至追蹤結束期間，嚴重度-持續時間分數降低了 57% (ZOSTAVAX 組的平均分數為 347，安慰劑組則為 805；p=0.016)。

為評估 ZOSTAVAX 對帶狀疱疹所造成之日常活動(ADL)干擾的影響，研究人員針對每一位受試者計算了一種以一般活動、情緒、行走能力、正常工作、與他人之關係、睡眠及生活樂趣所受到之干擾為基礎的綜合分數。每一個項目都是以 0 至 10 分的量表(0 分表示未受到任何干擾，10 分表示受到最大程度的干擾)進行評估。和安慰劑相比較，除了對帶狀疱疹的疫苗預防效果之外，ZOSTAVAX 亦可有利 (但不具統計意義)降低發生重大日常活動(ADL)干擾之風險(8%)的作用[重大日常活動(ADL)干擾定義為綜合 ADL 干擾分數 ≥ 2，且持續≥ 7 天]。在發生帶狀疱疹的接種者中，和安慰劑相比較，ZOSTAVAX 可使日常活動(ADL)干擾明顯降低。在 6 個月的追蹤期間，綜合日常活動(ADL)干擾方面的嚴重度-持續時間分數降低了 31% (ZOSTAVAX 組的平均分數為 57，安慰劑組則為 83；p=0.002)。

在帶狀疱疹發生後的 72 小時內，使用抗病毒藥物，並不會對 ZOSTAVAX 在帶狀疱疹相關疼痛或 PHN 之發生率方面所呈現的效果造成明顯的影響。在兩個接種組中，使用具鎮痛作用之藥物的病患比例大致相當。因此，使用這些藥物不太可能有助於降低帶狀疱疹相關疼痛或 PHN 的發生率。

整體來說，ZOSTAVAX對於PHN的預防效果主要來自疫苗對於帶狀疱疹的預防。在SPS研究中，在70歲以上的受試者族群，接種ZOSTAVAX可減低接種後發生PHN的機率。和接種安慰劑的受試者相比較，接種ZOSTAVAX的受試者較少通報其他特定帶狀疱疹相關併發症。在帶狀疱疹案例中，帶狀疱疹相關併發症在兩組中發生率相似(表2)。

表 2

在帶狀疱疹預防研究中發生帶狀疱疹之受試者所通報的

特定併發症*

併發症	ZOSTAVAX (N = 19,270)		安慰劑 (N = 19,276)	
	(n = 321)	% (於帶狀疱疹案例中)	(n = 659)	% (於帶狀疱疹案例中)
觸痛	135	42.1	310	47.0
細菌性繼發感染	3	0.9	7	1.1
病灶擴散	5	1.6	11	1.7

視覺損害**	2	0.6	9	1.4
周圍神經麻痺(運動神經)	5	1.6	12	1.8
眼瞼下垂**	2	0.6	9	1.4
留下疤痕	24	7.5	57	8.6
感覺喪失	7	2.2	12	1.8

N=接受隨機分組的受試人數

n=帶狀疱疹病例數，包括於接種後 30 天內所發生的病例，這部份的數據也有記錄可查

*在至少一個接種組之帶狀疱疹病例中的通報頻率≥1%的併發症。

**在接種 ZOSTAVAX 的受試者中有 35 位發生眼部帶狀疱疹，在接種安慰劑的受試者中有 69 位。

在發生帶狀疱疹的受試者中，肺炎、肝炎及腦膜腦炎等內臟併發症的通報率低於 1% (安慰劑組中有 3 個肺炎病例與 1 個肝炎病例，在疫苗組中有 1 個腦膜腦炎病例)。

ZOSTAVAX 的免疫生成性

在 ZOSTAVAX 療效及安全性研究（ZEST）中，隨機選取所收錄的 10%受試者（ZOSTAVAX 組 1,136 人，安慰劑組 1,133 人）評估其接種疫苗後所引發的免疫反應。接種 6 週後，和安慰劑相比較，ZOSTAVAX 可誘發較高的水痘帶狀疱疹病毒(VZV)特異性免疫反應。以醣蛋白酵素連結免疫吸附分析法（gpELISA）檢測而得的水痘帶狀疱疹病毒(VZV)抗體濃度（增加 2.3 倍, 95% CI[2.2, 2.4]有升高的現象。但目前還不知道抗體濃度到達多少時，可達到保護效果而不會發生帶狀疱疹。在帶狀疱疹預防研究(SPS)中，研究人員曾針對所收錄的部份受試者(N=1395)，評估接種疫苗所引發的免疫反應。接種 6 週後，和安慰劑相比較，ZOSTAVAX 可誘發較高的水痘帶狀疱疹病毒(VZV)特異性免疫反應。以醣蛋白酵素連結免疫吸附分析法(gpELISA)檢測而得的水痘帶狀疱疹病毒(VZV)抗體濃度(有 1.7 倍的差異，幾何平均濃度[GMT]分別為 479 與 288 個 gpELISA 單位/毫升，$p<0.001$)，以及以水痘帶狀疱疹病毒(VZV)干擾素-γ 酵素連結免疫斑點(IFN-γ ELISPOT)分析法檢測而得的 T 細胞活性(有 2.2 倍的差異，每百萬周邊血液單核細胞中之斑點形成細胞[SFC/10^6 PBMCs]的幾何平均計數[GMC]分別為 70 與 32，$p<0.001$)，都有升高的現象。

一項針對兩項評估接種 ZOSTAVAX 4 週後所引發之免疫反應的臨床試驗所進行的整合分析顯示，在 50 至 59 歲之受試者中(N=389)所引發的反應和≥ 60 歲的受試者(N=731)大致相當(GMT 分別為 668 與 614 個 gpELISA 單位/毫升)。在 50 至 59 歲的受試者中，依據 gpELISA 的檢測結果，接種疫苗後的免疫反應幾何平均升高倍數為 2.6 倍(95% CI：[2.4 至 2.9])，在≥ 60 歲的受試者中則為 2.3 倍(95% CI：[2.1 至 2.4])。

與其他疫苗同時接種後的免疫生成性

在一項雙盲對照性臨床試驗中，有 762 位 50 歲(含)以上的成人於隨機分組後接種一劑 ZOSTAVAX，並同時接種(N=382)或不同時接種(N=380)去活性流感疫苗。同時接種組中

的受試者係於第 1 天接種 ZOSTAVAX 與流感疫苗，並於第 4 週接種安慰劑。不同時接種組中的受試者係於第 1 天接種流感疫苗與安慰劑，並於第 4 週接種 ZOSTAVAX。在接種 4 週後，不論同時接種或不同時接種，兩種疫苗所引發的抗體反應都大致相當。

在一項雙盲對照性臨床試驗中，有 473 位 60 歲(含)以上的成人於隨機分組後接種一劑 ZOSTAVAX 並同時接種 PNEUMOVAX 23 (N=237) 或接種 PNEUMOVAX 23 後 4 週接種 ZOSTAVAX (N=236)。在接種 4 週後，兩種疫苗同時接種所引發的水痘帶狀疱疹病毒(VZV)抗體濃度顯著低於兩種疫苗不同時接種所引發的水痘帶狀疱疹病毒(VZV)抗體濃度(GMTs 分別為 338 與 484 個 gpELISA 單位/毫升; GMT 比例為 0.70 (95% CI: [0.61, 0.80]))。接種 4 週後，同時接種組與不同時接種組的水痘帶狀疱疹病毒(VZV)抗體濃度分別增加 1.9 倍(95% CI: [1.7, 2.1];符合已訂定的接受條件)與 3.1 倍(95% CI: [2.8, 3.5])。在兩組受試者中，PNEUMOVAX 23 抗體的 GMTs 相當。已證實同時接種 ZOSTAVAX 與 PNEUMOVAX 23 之安全性與兩疫苗不同時接種的安全性相似。

疫苗接種前曾得過帶狀疱疹之受試者的免疫生成性

在一項雙盲、安慰劑對照的隨機臨床試驗中，有 100 位 50 歲（含）以上曾得過帶狀疱疹的受試者接種一劑 ZOSTAVAX，接種 4 週後，和安慰劑相比較，ZOSTAVAX 可誘發明顯較高的水痘帶狀疱疹病毒(VZV)特異性免疫反應（有 2.1 倍的差異, 95% CI[1.5, 2.9]，P<0.001，幾何平均濃度[GMT]分別為 812 與 393 個 gpELISA 單位/毫升）。50 至 59 歲之受試者和≥ 60 歲的受試者的水痘帶狀疱疹病毒(VZV)抗體反應大致相當。

使用長期/維持性全身用皮質類固醇之受試者的免疫生成性

在一項雙盲、安慰劑對照的隨機臨床試驗中，有 206 位 60 歲（含）以上使用長期/維持性全身用皮質類固醇之受試者接種一劑 ZOSTAVAX，受試者在納入試驗之前至少使用兩週相當於每日劑量 5 至 20 毫克的 prednisone ，在接種後 6 週或更長時間評估 ZOSTAVAX 的免疫生成性及安全性。接種 6 週後，和安慰劑相比較，ZOSTAVAX 可誘發較高的水痘帶狀疱疹病毒(VZV)特異性 gpELISA 抗體幾何平均濃度（幾何平均濃度[GMT]分別為 531.1 與 224.3 個 gpELISA 單位/毫升）。依據 gpELISA 的檢測結果，ZOSTAVAX 組在接種疫苗前至接種後的水痘帶狀疱疹病毒(VZV)抗體反應幾何平均升高倍數為 2.3 倍(95% CI：[2.0 至 2.7])，安慰劑組則為 1.1 倍 (95% CI: [1.0 to 1.2])。(參見 **禁忌症**)

感染 HIV 之受試者的免疫生成性

在一項雙盲、安慰劑對照的隨機臨床試驗中，對感染人類免疫不全病毒(HIV)、接受強效複合式抗反轉錄病毒藥物治療且仍保有免疫功能(CD4+ T 細胞計數≥ 200 cells/μL)的成人患者(18 歲[含]以上)依兩劑接種時程施打 ZOSTAVAX。雖然這項研究採用兩劑接種時程，但 ZOSTAVAX 仍應依照單劑接種時程施打(參見**劑量與用法**)。在這項研究中，共有 295 位受試者接種第 1 劑，並有 286 位受試者接種第 2 劑。和安慰劑組相比較，ZOSTAVAX 在第 6 週(接種第 1 劑 6 週後)與第 12 週(接種第 2 劑 6 週後)所誘發的 VZV 特異性 gpELISA 抗體 GMT 都較高(GMT 分別為 534.4 與 530.3 個 gpELISA 單位/毫升，安慰劑組則為 263.7 與 250.3 個 gpELISA 單位/毫升)。在疫苗接種組中，依據 gpELISA 的檢測結果，第 6 週與第 12 週之 VZV 抗體反應相較於基線值的幾何平均升高倍數分別為 1.78 (95% CI：[1.64 至 1.92])與 1.80 (95% CI：[1.66 至 1.95])，在安慰劑接種組中則分別為 1.05 (95% CI：[0.98 至 1.12])與 1.04 (95% CI：[0.96 至 1.13])。(參見**禁忌症**中關於 HIV/AIDS 所引起之免疫抑制方面的說明)

SPS 短期持續性子研究(Short-term Persistence Substudy;STPS)

STPS的目的是獲得疫苗預防效果持續性的進一步資料並保留一部份受試者給長期持續性子研究(Long-term Persistence Substudy;LTPS)。STPS包含SPS中已接種ZOSTAVAX的7,320名受試者以及已接種安慰劑的6,950位受試者。於STPS開始收納時，受試者平均年齡為73.3歲。在STPS進行期間，給予安慰劑接種者ZOSTAVAX的時間點即為STPS完成的時間。

STPS對疫苗預防效果的分析是根據SPS研究中接種後4至7年為主的資料。STPS追蹤期的中位數為1.2年(1天至2.2年)。在STPS研究中，ZOSTAVAX組有84例可評估的帶狀疱疹(HZ)案例(觀察性帶狀疱疹發生率: 8.4/1000人年)，安慰劑組則有95例可評估的案例(觀察性帶狀疱疹發生率: 14/1000人年)。在STPS追蹤期間，對HZ發生率的估計疫苗帶狀疱疹預防效果為39.6% (18.2%, 55.5%)，對PHN發生率的估計疫苗預防效果為60.1% (-9.8%, 86.7%)，對HZ疼痛症狀疾病負擔(BOI)的估計疫苗預防效果則為50.1% (14.1%, 71.0%)。

SPS 長期持續性子研究(Long-term Persistence Substudy;LTPS)

STPS完成後，開放性的LTPS研究評估SPS研究的受試者中ZOSTAVAX對HZ, PHN及HZ疾病負擔(BOI)保護效果之持續時間。共有6,867位在SPS研究中接種ZOSTAVAX的受試者參與LTPS研究。於LTPS開始收納時，受試者平均年齡為74.5歲。

因為安慰劑接種者在 STPS 研究期間已接種疫苗，LTPS 研究在計算疫苗預防效果時無法得到同期性安慰劑控制組。因此，LTPS 研究在計算疫苗預防效果時，之前的安慰劑接種者是作為參考組。

LTPS對疫苗預防效果的分析是根據SPS研究中接種後7至10年為主的資料。LTPS研究追蹤期的中位數約為3.9年(一週至4.75年)。在LTPS研究中，有263例可評估的HZ案例發生於261位受試者(觀察性HZ發生率: 10.3/1000人年)。在LTPS追蹤期間，對HZ發生率的估計疫苗預防效果為21.1% (10.9%, 30.4%)，對PHN發生率的估計疫苗預防效果為35.4% (8.8%, 55.8%)，對HZ疼痛症狀疾病負擔(BOI)的估計疫苗預防效果則為37.3% (26.7%, 46.4%)。

適應症及說明

適應症：

ZOSTAVAX 適用於：

- 預防 50-79 歲之成人帶狀疱疹(皮蛇)

說明：

ZOSTAVAX適用於50-79歲之成人的免疫接種。

ZOSTAVAX 可與去活性流感疫苗同時接種(參見**劑量與用法**，以及**臨床藥理學**)。

禁忌症

曾對此疫苗的任何成分(包括明膠)產生過敏反應。

曾對 Neomycin (每劑泡製後的疫苗含有微量的 Neomycin)產生過敏/類過敏反應。Neomycin 過敏常會出現接觸性皮膚炎的表徵。不過，因使用 Neomycin 而發生接觸性皮膚炎的病史並非接種活性病毒疫苗的禁忌。

因下列疾病而呈現原發性或後天性的免疫不全狀態：急性與慢性白血病、淋巴瘤、其他會侵犯骨髓或淋巴系統的疾病、HIV/AIDS 所引起的免疫抑制(參見**臨床藥理學**及**副作用**)、細胞性免疫功能不全。

免疫抑制治療(包括高劑量的皮質類固醇)；不過，ZOSTAVAX 並不禁用於正在使用局部外用性/吸入性皮質類固醇或低劑量之全身用皮質類固醇的患者，或是正在使用皮質類固醇做為補充治療劑的患者，如腎上腺功能不全的患者。

未經治療的活動性結核病。

懷孕(參見**懷孕**)。

注意事項

醫護人員應向患者詢問其對先前所接種的任何含水痘帶狀疱疹病毒(VZV)成分的疫苗是否曾發生哪些反應(參見**禁忌症**)。

注射 ZOSTAVAX 後，曾有嚴重不良反應包括嚴重過敏性反應(anaphylaxis)發生。
和任何疫苗一樣，應預先做好適當的治療準備，包括腎上腺素注射劑(1:1000)，以便在發生過敏/類過敏反應時可立即使用。

在發燒>38.5°C (>101.3°F)的情況下，應考慮延後接種疫苗。

ZOSTAVAX 在已知感染人類免疫不全病毒(HIV)且併有或未併有免疫抑制現象之成人中的安全性與預防效果，目前尚未確立。針對人類免疫不全病毒(HIV)感染且仍保有免疫功能(CD4+ T 細胞計數≥ 200 cells/μL)的成人患者已完成一項第二期之安全性及免疫性研究(參見**臨床藥理學**及**副作用**)。

和任何疫苗一樣，接種 ZOSTAVAX 並不一定能對所有的接種者產生保護作用。

傳染

在 ZOSTAVAX 的臨床試驗中，並未出現疫苗病毒傳染的報告。不過，水痘疫苗的上市後使用經驗顯示，在發生水痘樣皮疹的疫苗接種者與具感受性的接觸者之間，可能會發生疫苗病毒傳染，但極為罕見。亦曾有未出現水痘樣皮疹的水痘疫苗接種者將疫苗病毒傳染給他人的報告。這是接種 ZOSTAVAX 的一個理論風險。應將減毒疫苗病毒傳染給具感受性者的風險和發生可能也會傳染給具感受性者之自然帶狀疱疹的風險放在一起權衡。

懷孕

目前尚未曾針對 ZOSTAVAX 進行過動物生殖研究。也不確知對孕婦施打 ZOSTAVAX 是否會造成胎兒傷害，或是否會影響生殖能力。不過，已知自然發生的水痘帶狀疱疹病毒

(VZV)感染有時會造成胎兒傷害。因此，ZOSTAVAX 不可施用於孕婦；此外，接種此疫苗後應避孕 3 個月(參見**禁忌症**)。

授乳母親

目前並不確知水痘帶狀疱疹病毒(VZV)是否會排入人類的乳汁。由於有些病毒會排入人類的乳汁，因此，對授乳婦女施打 ZOSTAVAX 時應謹慎。

小兒之使用

ZOSTAVAX 不建議用於此年齡群。

老年人之使用

在最大型(N=38,546)的 ZOSTAVAX 臨床研究中，所收錄之受試者的平均年齡為 69 歲(59-99 歲)。在 19,270 名接種 ZOSTAVAX 的受試者中，有 10,378 名為 60-69 歲、7,629 名為 70-79 歲、並有 1,263 名為 80 歲(含)以上。已證實 ZOSTAVAX 對此族群而言大致是安全而有效。

ZOSTAVAX 可使 60-69 歲與 70-79 歲之年齡層中的帶狀疱疹發生率分別降低 64% (95% CI：[56 至 71%])與 41% (95% CI：[28 至 52%])。疫苗接種者中的帶狀疱疹隨時間累計之發生率也有明顯降低的現象($p<0.001$；圖 1)。

藥物交互作用

ZOSTAVAX 不可與任何其他藥物混用於同一支針筒中。其他藥物必須使用不同的注射器施打於不同的身體部位。

目前尚未評估過將 ZOSTAVAX 和已知可有效對抗水痘帶狀疱疹病毒(VZV)之抗病毒藥物同時投予的結果。

ZOSTAVAX 與 PNEUMOVAX 23 不應同時接種，因為同時接種會導致 ZOSTAVAX 的免疫生成性降低。(參見**臨床藥理學**)

副作用

在臨床試驗中，研究人員曾針對超過 32,000 名 50 歲(含)以上的成人評估過 ZOSTAVAX 的一般安全性。ZOSTAVAX 通常具有良好的耐受性。

ZOSTAVAX 針對 50 至 59 歲受試者所做的療效及安全性研究（ZEST）

在 ZEST 研究中，不論是接種一劑 ZOSTAVAX（11,184 人）或安慰劑（11,212 人）的受試者，在研究期間都會進行安全性監測。研究期間，ZOSTAVAX 組曾出現一例與疫苗相關之嚴重不良反應（過敏反應）的報告。

所有的受試者除了在整個研究期間定期接受安全性的監視之外，都會利用疫苗接種報告卡（VRC）來記錄接種後 0 至 42 天期間所發生的不良事件。

在 ZEST 研究中，曾發生下列極常見(≥ 1/10)與常見(≥ 1/100 但<1/10)之疫苗相關注射部位不良事件與全身性不良事件的報告。有些不良事件是徵詢而得的結果(接種後 1 至 5 天)，這些不良反應皆以星號(*)註明。

神經系統疾患

*常見：*頭痛

全身性症狀與投藥部位反應

*極常見：*紅斑*、疼痛*、腫脹*、搔癢

*常見：*血腫、溫熱感、硬結

肌肉骨骼及結締組織疾患

常見：四肢疼痛

在接種 ZOSTAVAX 的受試者中，疫苗相關注射部位不良事件的整體發生率要明顯高於接種安慰劑的受試者（ZOSTAVAX 組為 63.9%，安慰劑組為 14.4%）。

在 ZEST 研究的 42 天接種後通報期間，出現非注射部位之帶狀疱疹樣皮疹的病例數有 34 例（ZOSTAVAX 組 19 例，安慰劑組 15 例）。其中 24 例組織樣本適合進行 PCR 試驗，這些組織樣本中有 10 例被檢出野生型水痘帶狀疱疹病毒(VZV)（ZOSTAVAX 組 3 例，安慰劑組 7 例)。但這些組織樣本中皆未檢出 Oka/Merck 株水痘帶狀疱疹病毒(VZV)。

在同樣的 ZEST 研究的 42 天接種後通報期間，發生水痘樣皮疹的通報病例數有 124 例（ZOSTAVAX 組 69 例，安慰劑組 55 例）。其中有 23 例可取得組織樣本且適合進行 PCR 試驗。這些組織樣本中，ZOSTAVAX 組有 1 例被檢出水痘帶狀疱疹病毒(VZV)；然而，其病毒株無法被確認（野生株或 Oka/Merck 株）。

針對 60 歲（含）以上受試者所進行的帶狀疱疹預防研究(Shingles Prevention Study; SPS)

其中最大型的試驗(帶狀疱疹預防研究[SPS])中，共有 38,546 位受試者分別接種了一劑的 ZOSTAVAX (n=19,270)或安慰劑(n=19,276)，並在整個研究期間接受安全性的監視。在研究期間，有 2 位接種 ZOSTAVAX 的受試者(氣喘惡化及風濕性多發肌痛症)及 3 位接種安慰劑的受試者(Goodpasture 氏症候群、過敏性反應、以及風濕性多發肌痛症)通報發生和疫苗有關的嚴重不良事件。

在不良事件監視子研究中，有部份參與 SPS 研究的子群受試者(ZOSTAVAX 組 n=3,345，安慰劑組 n=3,271)除了在整個研究期間定期接受安全性的監視之外，並利用疫苗接種報告卡(VRC)來記錄接種後 0 至 42 天期間所發生的不良事件。

在不良事件監視子研究中，曾有發生下列極常見(≥ 1/10)與常見(≥ 1/100 但<1/10)之疫苗相關注射部位不良事件與全身性不良事件的報告。這些不良事件大部份都是輕度的反應。有些不良事件是徵詢而得的結果(接種後 0 至 4 天)，這些不良反應皆以星號(*)註明。

神經系統疾患

*常見：*頭痛

全身性症狀與投藥部位反應

*極常見：*紅斑*、疼痛/觸痛*、腫脹*

*常見：*血腫、搔癢、溫熱感

在接種 ZOSTAVAX 的受試者中，疫苗相關注射部位不良事件的整體發生率要明顯高於接種安慰劑的受試者(ZOSTAVAX 組為 48%，安慰劑組為 17%)。

SPS 研究中的其餘受試者都接受定期的安全性監視，但未使用報告卡。這些受試者所通報之事件的類型和不良事件監視子研究中的子群受試者大致相同。

在 SPS 研究的 42 天接種後通報期間，通報發生帶狀疱疹樣皮疹的病例數在所有受試者中都很少(ZOSTAVAX 組有 17 例，安慰劑組有 36 例；p=0.009)。在這 53 個帶狀疱疹樣皮疹病例中，有 41 例可取得組織樣本且適合進行 PCR 試驗。其中有 25 例組織樣本檢出野生型水痘帶狀疱疹病毒(VZV) (ZOSTAVAX 組有 5 例，安慰劑組有 20 例)。在這些組織樣本中皆未檢出 Oka/Merck 株水痘帶狀疱疹病毒(VZV)。

在同樣的 SPS 研究的 42 天接種後通報期間，發生水痘樣皮疹的通報病例數也很少(n=59)。在這些水痘樣皮疹病例中，有 10 例可取得組織樣本且適合進行 PCR 試驗。在這些組織樣本中皆未檢出水痘帶狀疱疹病毒(VZV)。

其他的研究

在其他支持 ZOSTAVAX 冷凍配方藥證核准的臨床試驗中，帶狀疱疹疫苗接種者與安慰劑接種者於接種後 42 天內通報發生非注射部位帶狀疱疹樣皮疹及水痘樣皮疹的比率也都很低。在 17 名通報發生水痘樣皮疹及非注射部位帶狀疱疹樣皮疹的病例中，有 10 例可取得組織樣本且適合進行 PCR 試驗，有 2 名受試者其水痘確認為 Oka/Merck 株病毒。

在針對 50 歲(含)以上之受試者進行評估的 ZOSTAVAX 臨床試驗中，包括一項同時施打去活性流感疫苗的研究，其安全性表現和在 SPS 研究之不良事件監視子研究中所見者大致相當。不過，在這些試驗中，50-59 歲之受試者通報發生輕至中度注射部位不良事件的比率要比≥ 60 歲的受試者高。

在一項雙盲、安慰劑對照的隨機臨床試驗中，給予 100 位 50 歲（含）以上曾得過帶狀疱疹的受試者接種一劑 ZOSTAVAX，以評估 ZOSTAVAX 的免疫生成性及安全性。在這項臨床研究中，其安全性與 SPS 不良事件監視子研究所得到的結果大致相當。

在一項雙盲、安慰劑對照的隨機臨床試驗中，有 206 位 60 歲（含）以上使用長期/維持性全身用皮質類固醇之受試者接種一劑 ZOSTAVAX，受試者在納入試驗之前至少使用兩週相當於每日劑量 5 至 20 毫克的 prednisone ，在接種後 6 週或更長時間評估 ZOSTAVAX 的免疫生成性及安全性。所有接種疫苗的受試患者都必須接受不良事件的追蹤。由研究人員依據盲性資料來判定疫苗相關性。為評估與研究疫苗短暫相關的不良事件，患者在疫苗接種後第 1 天至第 42 天期間必須使用疫苗接種報告卡(VRC)記錄所發生

的任何注射部位不良事件、全身性不良事件、體溫升高及皮疹。在整個研究期間(即疫苗接種後第 182 天)都會追蹤患者是否發生嚴重不良事件，不論該事件是否與研究疫苗相關。在這項臨床研究中，其安全性與 SPS 不良事件監視子研究所得到的結果大致相當。(參見**禁忌症**)

在一項雙盲、安慰劑對照的隨機臨床試驗中，對感染人類免疫不全病毒(HIV)、接受強效複合式抗反轉錄病毒藥物治療且仍保有免疫功能(CD4+ T 細胞計數≥ 200 cells/μL)的成人患者(18 歲[含]以上)依兩劑接種時程施打 ZOSTAVAX。雖然這項研究採用兩劑接種時程，但 ZOSTAVAX 仍應依照單劑接種時程施打(參見**劑量與用法**)。在這項臨床試驗中，共有 295 位受試者接種第 1 劑，並有 286 位受試者接種第 2 劑。所有接種疫苗的受試患者都必須接受不良事件的追蹤。由研究人員依據盲性資料來判定疫苗相關性。為評估與研究疫苗短暫相關的不良事件，患者在每次疫苗接種後的 6 週期間必須使用疫苗接種報告卡(VRC)記錄所發生的任何注射部位不良事件、全身性不良事件、體溫升高及皮疹。在整個研究期間(即疫苗接種後第 24 週)都會追蹤患者是否發生嚴重不良事件，不論該事件是否與研究疫苗相關。在這項臨床研究中，其安全性表現與 SPS 不良事件監視子研究所得到的結果大致相當。(參見**禁忌症**中關於 HIV/AIDS 所引起之免疫抑制方面的說明)

為因應不知是否曾接種過 ZOSTAVAX 之接種者的顧慮，研究人員曾針對接種第二劑 ZOSTAVAX 的安全性與耐受性進行評估。在一項安慰劑對照性雙盲研究中，有 98 位 60 歲(含)以上的成人於接種第一劑 ZOSTAVAX 的 42 天後接種了第二劑，結果顯示此疫苗的耐受性大致相當良好。接種第二劑 ZOSTAVAX 後的疫苗相關不良事件的發生率和接種第一劑時所見者大致相當。

上市後的使用經驗

在 ZOSTAVAX 的上市後的使用經驗中，曾發現下列這些其他的不良反應。由於這些反應都是源自不特定大小之族群的主動通報，因此通常無法確實估算其發生頻率或確立其與疫苗的因果關係。

胃腸疾患: 噁心。
感染與寄生蟲疾病： 帶狀疱疹(疫苗株)。
皮膚與皮下組織疾患： 皮疹。
肌肉骨骼與結締組織疾患： 關節痛、肌痛。
全身性症狀與投藥部位反應： 注射部位皮疹、注射部位蕁麻疹、發燒、暫時性注射部位淋巴結病。

*免疫系統疾患：*過敏反應，包括過敏性反應。

過量

目前並無任何關於使用過量方面的資料。

劑量與用法

僅供皮下注射使用。

切勿以靜脈注射的方式施打。

接種者應接種單一劑量。目前並不確知接種 ZOSTAVAX 後之保護效果的持續時間。在帶狀疱疹預防研究(SPS)中，已證實 4 年追蹤期的保護效果。再次接種的必要性尚未確立。

ZOSTAVAX 並非帶狀疱疹或 PHN 的治療劑。

ZOSTAVAX 可與去活性流感疫苗同時施打，但應使用不同的針筒。

自冰箱中取出後應立即進行泡製。

泡製此疫苗時，僅可使用原廠提供的稀釋液，因為此稀釋液完全不含防腐劑或其他可能會使疫苗病毒失去活性的抗病毒物質。
本疫苗之稀釋液有"小瓶裝稀釋液"及"預充針筒裝稀釋液"兩種不同包裝，其使用方法分別說明如下：
小瓶裝稀釋液：
泡製此疫苗時，應先將稀釋液小瓶中的內容物全部抽入針筒。將針筒中的稀釋液全部注入裝有冷凍乾燥疫苗的小瓶中，然後輕輕搖動，使其混合均勻。將內容物全部抽入針筒，然後將泡製後的疫苗以皮下注射的方式全部注入體內，最好是注入上臂(以三角肌部位為佳)。

預充針筒裝稀釋液：

泡製此疫苗時，應將針筒中的稀釋液全部注入裝有冷凍乾燥疫苗的小瓶中，然後輕輕搖動，使其混合均勻。將內容物全部抽入針筒，然後將泡製後的疫苗以皮下注射的方式全部注入體內，最好是注入上臂(以三角肌部位為佳)。

建議此疫苗在泡製後應立即施打，以免效價減弱。泡製後的疫苗若未在 30 分鐘內使用，即應予以拋棄。

泡製後的疫苗切勿冷凍。

注意：每次施打及(或)泡製 ZOSTAVAX 時，皆應使用不含防腐劑、殺菌劑及清潔劑的無菌針筒，因為這些物質可能會使疫苗病毒失去活性。

施打 ZOSTAVAX 時應使用一套獨立的無菌針頭與針筒，以避免傳染感染性疾病。

針頭應依規定正確處理，且不可套回針頭蓋。

在溶液與容器許可的情況下，注射藥品在施打前都應目視檢查是否有外來異物或變色的現象。ZOSTAVAX 在泡製後會形成一種半透明至透明的灰白色至淡黃色液體。

包裝規格

每盒 1 支 1 劑量小瓶的凍晶乾粉疫苗及 1 小瓶裝稀釋液。
每盒 1 支 1 劑量小瓶的凍晶乾粉疫苗及 1 支針筒裝稀釋液(附或不附針頭)。
每盒 10 支 1 劑量小瓶的凍晶乾粉疫苗及分開盒裝 10 小瓶稀釋液。
每盒 10 支 1 劑量小瓶的凍晶乾粉疫苗及 10 支針筒裝稀釋液(附或不附針頭)。

貯存

貯存
在運送期間，為確保效價不致流失，應將此疫苗保存於 8°C (46°F)或更低的溫度下。

ZOSTAVAX **應冷藏貯存**於 2 至 8°C (36 至 46°F)或更低的溫度下，直到準備泡製成注射液再取出(參見**劑量與用法**)。稀釋液應另外貯存於室溫下(20 至 25°C，68 至 77°F)或冰箱中(2 至 8°C，36 至 46°F)。

在泡製之前應避免光線照射。

泡製後的疫苗若未在 30 分鐘內使用，即應予以拋棄。

泡製後的疫苗切勿冷凍。

製造廠：Merck Sharp & Dohme Corp.
廠址：770 Sumneytown Pike, West Point, PA 19486, U.S.A.
針筒裝稀釋液製造廠：VETTER PHARMA-FERTIGUNG GMBH & CO. KG
廠址：Schutzenstrasse 87, D-88212 Ravensburg, Germany
小瓶裝稀釋液製造廠：Jubilant HollisterStier LLC (Small Volume Parenteral Facilities)
廠址：3525 North Regal Street, Spokane, WA 99207, U.S.A.
包裝廠： MERCK SHARP & DOHME B.V.
廠址：Waarderweg 39, 2031 BN Haarlem, The Netherlands

藥商：美商默沙東藥廠股份有限公司台灣分公司
地址：台北市信義路五段 106 號 12 樓

ZOSTAVAX™

Zoster Virus Vaccine Live (Oka/Merck)

Refrigerator-stable formulation

V211-TWN-2015-010820

Description

ZOSTAVAX® is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV). The virus was initially obtained from a child with naturally-occurring varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Further passage of the virus was performed at Merck Research Laboratories (MRL) in human diploid cell cultures (MRC-5) that were free of adventitious agents. This live, attenuated zoster vaccine is a lyophilized preparation containing sucrose, phosphate, glutamate, and processed gelatin as stabilizers.

ZOSTAVAX, when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.65-mL dose contains a minimum of 19,400 PFU (plaque-forming units) of Oka/Merck VZV when reconstituted and stored at room temperature for up to 30 minutes.

Each 0.65-mL dose contains: 41.05 mg of sucrose, 20.53 mg of hydrolyzed porcine gelatin, 8.55 mg of urea, 5.25 mg of sodium chloride, 0.82 mg of monosodium L-glutamate, 0.75 mg of sodium phosphate dibasic, 0.13 mg of potassium phosphate monobasic, 0.13 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin and bovine calf serum. The product contains no preservative.

CLINICAL PHARMACOLOGY

Herpes Zoster

Herpes zoster (HZ), commonly known as shingles or simply " zoster," is a manifestation of the reactivation of VZV, which, as a primary infection, produces chickenpox (varicella). Following initial infection, the virus remains latent in the dorsal root or cranial sensory ganglia until it reactivates, producing zoster. Zoster is usually characterized by a unilateral, painful, vesicular cutaneous eruption with a dermatomal distribution.

Although the blistering rash is the most distinctive feature of zoster, the most frequently debilitating symptom is pain, which may occur during the prodrome, the acute eruptive phase, and the postherpetic phase of the infection. During the acute eruptive phase, local pain has been reported to occur in up to 90% of immunocompetent individuals.

Anyone who has been infected with VZV, including those without a clinical history of varicella, is at risk for developing zoster, which is considered to be due to waning immunity to VZV. Nearly all adults (~98%) in the U.S. are susceptible to zoster, where an estimated 1 million cases occur annually. This number is expected to rise as the mean age of the population increases. The incidence and severity of zoster, as well as the frequency and severity of its complications, increase markedly with age, with two-thirds of the cases occurring in individuals older than 50 years of age. In recent studies, the lifetime risk of zoster has been estimated to be as high as 30% in the general population. It is estimated that by 85 years of age, 50% of individuals will have experienced an episode of zoster.

Seventy to 80% of hospitalizations for zoster occur among immunocompetent individuals. In the U.S., approximately 50,000 to 60,000 zoster-associated hospitalizations, including 12,000 to 19,000 in which the primary diagnosis is zoster, occur each year.

Zoster may be associated with serious complications, such as postherpetic neuralgia (PHN), scarring, bacterial superinfection, motor neuron palsies, pneumonia, encephalitis, Ramsay Hunt syndrome, visual impairment, hearing loss, and death.

Zoster-associated pain and discomfort can be prolonged and disabling and can diminish quality of life and functional capacity to a degree comparable to such debilitating diseases as congestive heart failure, myocardial infarction, type II diabetes mellitus, and major depression.

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) constitutes the most common serious complication and cause of zoster-associated morbidity in the immunocompetent host. Published literature estimates the prevalence of PHN in the U.S. population to be 500,000 to 1,000,000 cases. The frequency and severity of PHN increase with age, and may complicate 25 to 50% of zoster cases among patients over 50 years of age. PHN has been described as tender, burning, throbbing, stabbing, shooting and/or sharp pain that can persist for months or even years and can also lead to emotional distress. Allodynia (pain from an innocuous stimulus) is present in at least 90% of patients with PHN and is typically described as one of the most distressing and debilitating types of pain. Several definitions of PHN are widely used in the medical community, including pain persisting longer than 90 days after the onset of the rash.

Mechanism of Action

The risk of developing zoster appears to be causally related to a decline in VZV-specific immunity. ZOSTAVAX was shown to boost VZV-specific immunity, which is thought to be the mechanism by which it protects against zoster and its complications. (See *Immunogenicity*.)

Clinical Studies

Evaluation of Clinical Efficacy Afforded by ZOSTAVAX

ZOSTAVAX Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age

In the ZOSTAVAX Efficacy and Safety Trial (ZEST), a placebo-controlled, double-blind clinical trial in which 22,439 subjects 50 to 59 years of age were randomized to receive a single dose of either ZOSTAVAX (n=11,211) or placebo (n=11,228) and were followed for the development of zoster for a median of 1.3 years (range 0 to 2 years). All suspected zoster cases were adjudicated by a clinical evaluation committee. Final determination of zoster cases was made by Polymerase Chain Reaction (PCR) [86%], or in the absence of virus detection, as determined by a clinical evaluation committee [14%].

ZOSTAVAX significantly decreased the incidence of zoster compared with placebo (30 cases [2.0/1000 person-years] vs. 99 cases [6.6/1000 person-years], respectively; $p<0.001$). The protective efficacy of ZOSTAVAX against zoster was 69.8% (95% CI: [54.1 to 80.6%]).

Shingles Prevention Study (SPS) in Subjects 60 Years of Age and Older

In the Shingles Prevention Study (SPS), a placebo-controlled, double-blind clinical trial of ZOSTAVAX, 38,546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276) and were followed for the development of zoster for an average of 3.1 years (range 1 day to 4.9 years). Randomization was stratified by age, 60-69 and ≥ 70 years of age. All suspected zoster cases were adjudicated by a clinical evaluation committee. Final determination of zoster cases was made by PCR, local culture, or the decision of the clinical evaluation committee, in that order. In both vaccination groups (ZOSTAVAX and placebo), subjects who developed zoster were given famciclovir, and as necessary, pain medications. Severity of pain was evaluated according to a " worst pain" score on a 0-to-10 scale, using the Zoster Brief Pain Inventory (ZBPI), a validated questionnaire. A score of 3 or higher was considered clinically significant because it correlates with significant interference with activities of daily living (ADL).

ZOSTAVAX significantly reduced the risk of developing zoster and PHN compared with placebo. In addition, ZOSTAVAX significantly reduced acute and chronic zoster-associated pain as measured by the HZ pain burden of illness (BOI) score. (See Table 1.)

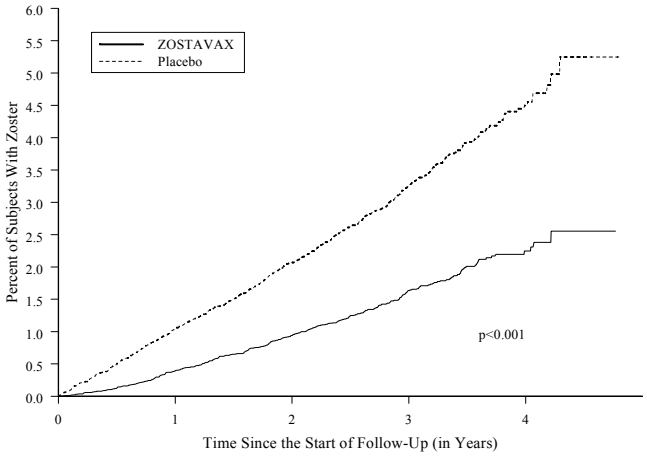
Table 1
Efficacy of ZOSTAVAX Compared with Placebo
in the Shingles Prevention Study

Endpoint	Vaccine efficacy	95% CI
Incidence of Zoster	51%	44 to 58%
Incidence of PHN*	67%	48 to 79%
HZ Pain BOI**	61%	51 to 69%

*Clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash.
**The HZ pain BOI score is a composite score that incorporates the incidence, severity, and duration of acute and chronic zoster-associated pain over a 6-month follow-up period.

ZOSTAVAX significantly decreased the incidence of zoster compared with placebo (315 cases [5.4/1000 person-years] vs. 642 cases [11.1/1000 person-years], respectively; p<0.001). The protective efficacy of ZOSTAVAX against zoster was 51% (95% CI: [44 to 58%]). ZOSTAVAX reduced the incidence of zoster by 64% (95% CI: [56 to 71%]) in individuals 60-69 years of age and by 41% (95% CI: [28 to 52%]) in individuals 70 to 79 years of age. The cumulative incidence of zoster over time among vaccine recipients was also significantly reduced (p<0.001; Figure 1).

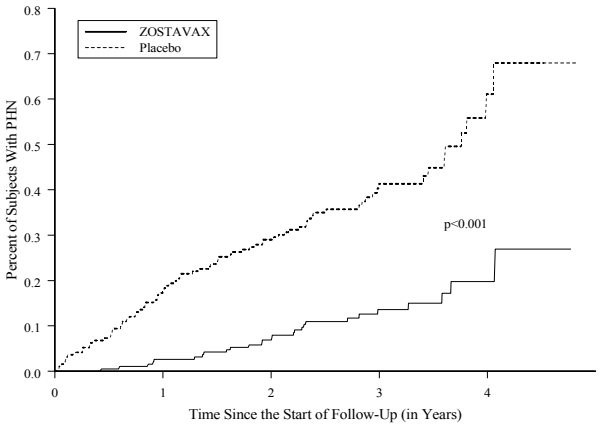
Figure 1
Kaplan-Meier Plot of the Cumulative Incidence of Zoster Over Time*
in the Shingles Prevention Study



*A limited number of subjects were followed beyond Year 4.

ZOSTAVAX decreased the incidence of PHN compared with placebo (27 cases [0.5/1000 person-years] vs. 80 cases [1.4/1000 person-years], respectively; p<0.001). In this trial, the definition of PHN was clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash. The protective efficacy of ZOSTAVAX against PHN was 67% (95% CI: [48 to 79%]), and the reduction was similar for the two age groups (60-69 and ≥ 70 years of age). In addition, the efficacy of ZOSTAVAX did not change appreciably when PHN was defined using alternative cutoff times (30, 60, 120, or 182 days) for duration of pain. ZOSTAVAX significantly reduced the cumulative incidence of PHN over time compared with placebo (p<0.001; Figure 2).

Figure 2
Kaplan-Meier Plot of the Cumulative Incidence of PHN Over Time*
in the Shingles Prevention Study



*A limited number of subjects were followed beyond Year 4.

The protective efficacy of ZOSTAVAX against PHN among HZ cases, or the vaccine effect on incidence of PHN above and beyond its effect on incidence of HZ, was 39% (95% CI: [7 to 59%]). For those in the 70 to 79 years of age group, there was a statistically significant relative reduction of PHN following HZ conferred by ZOSTAVAX. The protective efficacy in this age group was 55% (95% CI: [18 to 76%]).

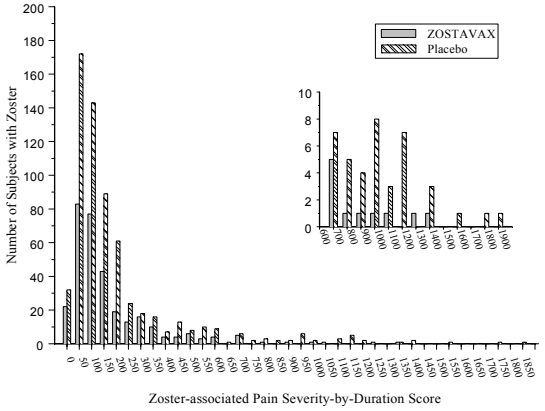
ZOSTAVAX reduced the HZ pain BOI score by approximately 61% (95% CI: [51 to 69%]), compared with placebo. ZOSTAVAX reduced the HZ pain BOI score to a similar extent for the two age groups (60-69 and ≥ 70 years of age). The HZ pain BOI score is a composite score that incorporates the incidence, severity, and duration of acute and chronic zoster-associated pain over a 6-month follow-up period.

ZOSTAVAX reduced the incidence of severe and long-lasting zoster-associated pain (severity-by-duration score >600) by 73% (95% CI: [46 to 87%]) compared with placebo. Eleven subjects vaccinated with ZOSTAVAX had severity-by-duration scores >600, compared with 40 subjects who received placebo. (See Figure 3.)

Among vaccinated individuals who developed zoster, ZOSTAVAX significantly reduced zoster-associated pain compared with placebo. Over the 6-month follow-up period, there was a 22% reduction in the severity-by-duration score (average scores of 141 for ZOSTAVAX and 181 for placebo; p=0.008).

Figure 3

Zoster-associated Pain Severity-by-Duration Score Over Time in the Shingles Prevention Study*



*The inset presents the number of subjects with severity-by-duration score >600. For example, a daily worst pain rated at the maximum score of 10 for >60 days would result in a severity-by-duration score of >600.

Among vaccinated individuals who developed PHN, ZOSTAVAX significantly reduced PHN-associated pain compared with placebo. In the period from 90 days after rash onset to the end of follow-up, there was a 57% reduction in the severity-by-duration score (average scores of 347 for ZOSTAVAX and 805 for placebo; p=0.016).

To evaluate the impact of ZOSTAVAX on ADL interference associated with zoster, a combined score was calculated for each subject based on interference with general activity, mood, walking ability, normal work, relations with others,

sleep, and enjoyment of life. Each item was measured on a 0-to-10 scale (0 being no interference and 10 being maximum interference). Compared to placebo, ZOSTAVAX led to a favorable, but not statistically significant, reduction (8%) in the risk of having substantial ADL interference (defined as having a combined ADL interference score ≥ 2 for ≥ 7 days) beyond the vaccine efficacy for zoster. Among vaccinated individuals who developed zoster, ZOSTAVAX significantly reduced ADL interference compared with placebo. Over the 6-month follow-up period, there was a 31% reduction in the severity-by-duration score for combined ADL interference (average scores of 57 for ZOSTAVAX and 83 for placebo; p=0.002).

The use of antiviral drugs within 72 hours of zoster rash onset did not have a significant effect on the efficacy of ZOSTAVAX for zoster pain or PHN incidence. The proportions of subjects using medications with analgesic effects were balanced between vaccination groups. Therefore, the use of these medications was not likely to have contributed to the reduction of zoster pain or PHN incidence.

Overall, the benefit of ZOSTAVAX in the prevention of PHN can be primarily attributed to the effect of the vaccine on the prevention of herpes zoster. Vaccination with ZOSTAVAX in the SPS reduced the incidence of PHN in individuals 70 years of age and older who developed zoster postvaccination. Other prespecified zoster-related complications were reported less frequently in subjects who received ZOSTAVAX compared to subjects who received placebo. Among HZ cases, zoster-related complications were reported at similar rates in both vaccination groups (Table 2).

Table 2
Specific complications* of zoster among HZ cases in the Shingles Prevention Study

Complication	**ZOSTAVAX** (N = 19,270)		**Placebo** (N = 19,276)	
	(n = 321)	% among zoster cases	(n = 659)	% among zoster cases
Allodynia	135	42.1	310	47.0
Bacterial Superinfection	3	0.9	7	1.1
Dissemination	5	1.6	11	1.7
Impaired Vision**	2	0.6	9	1.4
Peripheral Nerve Palsies (motor)	5	1.6	12	1.8
Ptosis**	2	0.6	9	1.4
Scarring	24	7.5	57	8.6
Sensory Loss	7	2.2	12	1.8

N=number of subjects randomized
n=number of zoster cases, including those cases occurring within 30 days postvaccination, with these data available
*Complications reported at a frequency of ≥ 1% in at least one vaccination group among subjects with zoster.
**Ophthalmic zoster occurred in 35 subjects vaccinated with ZOSTAVAX vs. 69 subjects who received placebo.

Visceral complications such as pneumonitis, hepatitis, and meningoencephalitis were reported by fewer than 1% of subjects with zoster (3 cases of pneumonitis and 1 case of hepatitis in the placebo group; 1 case of meningoencephalitis in the vaccine group).

Immunogenicity of ZOSTAVAX

Within the ZOSTAVAX Efficacy and Safety Trial (ZEST), immune responses to vaccination were evaluated in a random 10% subcohort (n=1,136 for ZOSTAVAX and n=1,133 for placebo) of the subjects enrolled in the ZEST. ZOSTAVAX elicited higher VZV-specific immune responses at 6 weeks postvaccination compared with placebo. Increases in VZV antibody level, measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) were demonstrated (2.3-fold

difference (95% CI [2.2, 2.4]). However, the cutoff value in antibody level that is associated with protection against HZ is unknown at present.

Within the Shingles Prevention Study (SPS), immune responses to vaccination were evaluated in a subset of the enrolled subjects (N=1395). ZOSTAVAX elicited higher VZV-specific immune responses at 6 weeks postvaccination compared with placebo. Increases in both VZV antibody level, measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) (1.7 fold-difference, geometric mean titer [GMT] of 479 vs. 288 gpELISA units/mL, p <0.001), and T-cell activity, measured by VZV interferon-gamma enzyme-linked immunospot (IFN-γ ELISPOT) assay (2.2 fold-difference, geometric mean count [GMC] of 70 vs. 32 spot-forming cells per million peripheral blood mononuclear cells [SFC/10^6 PBMCs], p<0.001) were demonstrated.

In an integrated analysis of two clinical trials evaluating immune response to ZOSTAVAX at 4 weeks postvaccination, responses were generally similar in subjects 50 to 59 (N=389) compared to subjects ≥ 60 years of age (N=731) (GMT of 668 vs. 614 gpELISA units/ml, respectively). The geometric mean fold-rise of immune response following vaccination as measured by gpELISA was 2.6-fold (95% CI: [2.4 to 2.9]) in subjects 50 to 59 years of age and 2.3-fold (95% CI: [2.1 to 2.4]) in subjects ≥ 60 years age.

Immunogenicity following concomitant administration

In a double-blind, controlled clinical trial, 762 adults 50 years of age and older were randomized to receive a single dose of ZOSTAVAX administered either concomitantly (N=382) or nonconcomitantly (N=380) with inactivated influenza vaccine. Subjects enrolled in the concomitant group received ZOSTAVAX and influenza vaccine on Day 1 and placebo at Week 4. Subjects enrolled in the nonconcomitant group received influenza vaccine and placebo on Day 1 and ZOSTAVAX at Week 4. The antibody responses to both vaccines at 4 weeks postvaccination were similar, whether administered concomitantly or nonconcomitantly.

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomized to receive ZOSTAVAX and PNEUMOVAX 23 concomitantly (N=237), or PNEUMOVAX 23 alone followed 4 weeks later by ZOSTAVAX alone (N=236). At four weeks postvaccination, the VZV antibody levels following concomitant use were significantly lower than the VZV antibody levels following nonconcomitant administration (GMTs of 338 vs. 484 gpELISA units/mL, respectively; GMT ratio = 0.70 (95% CI: [0.61, 0.80])). VZV antibody levels 4 weeks postvaccination were increased 1.9-fold (95% CI: [1.7, 2.1]; meeting the pre-specified acceptance criterion) in the concomitant group vs. 3.1-fold (95% CI: [2.8, 3.5]) in the nonconcomitant group. The GMTs for PNEUMOVAX 23 antigens were comparable between the two groups. Concomitant use of ZOSTAVAX and PNEUMOVAX 23 demonstrated a safety profile that was generally similar to that of the two vaccines administered nonconcomitantly.

Immunogenicity in subjects with a history of herpes zoster (HZ) prior to vaccination

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 100 subjects 50 years of age or older with a history of herpes zoster (HZ) prior to vaccination to assess immunogenicity of ZOSTAVAX. ZOSTAVAX induced a significantly higher VZV-specific immune response as measured by gpELISA at 4 weeks postvaccination, compared with placebo (2.1-fold difference (95% CI: [1.5 to 2.9], p<0.001, GMT of 812 vs. 393 gpELISA units/ml). VZV antibody responses were generally similar in subjects 50 to 59 compared to subjects ≥ 60 years of age.

Immunogenicity in subjects on chronic/maintenance systemic corticosteroids

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrollment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of ZOSTAVAX. Compared with placebo, ZOSTAVAX induced a higher VZV-specific gpELISA antibody GMT at 6 weeks postvaccination (GMT of 531.1 vs. 224.3 gpELISA units/ml, respectively). The geometric mean fold-rise of the VZV antibody response, as measured by gpELISA, from prevaccination to postvaccination was 2.3 (95% CI: [2.0 to 2.7]) in the ZOSTAVAX group compared to 1.1 (95% CI: [1.0 to 1.2]) in the placebo group (See **CONTRAINDICATIONS** regarding corticosteroids)

Immunogenicity in subjects with HIV infection

In a double-blind, placebo-controlled randomized clinical trial, ZOSTAVAX was administered as a two-dose regimen to human immunodeficiency virus (HIV)-infected adults (18 years of age or older) on potent combination antiretroviral therapy with conserved immune function (CD4+ T cell count ≥ 200 cells/μL). Although a two-dose regimen was used in this study, ZOSTAVAX is administered as a single dose regimen (see DOSAGE & ADMINISTRATION). In this study, a total of 295 subjects received dose 1 and 286 subjects received dose 2. Compared with placebo, ZOSTAVAX induced a higher VZV-specific gpELISA antibody GMT at Week 6 (6 weeks following dose 1) and Week 12 (6 weeks following dose 2) (GMT of 534.4 and 530.3 vs. 263.7 and 250.3 gpELISA units/ml, respectively). The geometric mean fold-rises of the VZV antibody response, as measured by gpELISA, from baseline to Week 6 and Week 12 were 1.78 (95% CI: [1.64 to 1.92]) and 1.80 (95% CI: [1.66 to 1.95]), respectively, in vaccine recipients and 1.05 (95% CI: [0.98 to 1.12]) and 1.04 (95% CI: [0.96 to 1.13]), respectively, in placebo recipients. (See CONTRAINDICATIONS regarding immunosuppression due to HIV/AIDS.)

The SPS Short-term Persistence Substudy (STPS)

The STPS was initiated to accrue additional information on the persistence of vaccine efficacy and to preserve a subset of subjects for the long-term persistence substudy (LTPS).The STPS included 7,320 subjects previously vaccinated with ZOSTAVAX and 6,950 subjects previously vaccinated with placebo in the SPS. The mean age at enrollment in STPS was 73.3 years. During the course of STPS, placebo recipients were offered ZOSTAVAX, at which time they were considered to have completed the STPS.

The STPS analyses for vaccine efficacy are based on data collected primarily 4 to 7 years postvaccination in the SPS. The median follow-up in the STPS was ~1.2 years (range is one day to 2.2 years). In the STPS, there were 84 evaluable HZ cases in the ZOSTAVAX group (observed HZ incidence rate: 8.4 per 1000 Person-Years) and 95 evaluable cases in the placebo group (observed HZ incidence rate: 14 per 1000 Person-Years). The estimated vaccine efficacy for HZ incidence during the STPS follow-up period was 39.6% (18.2%, 55.5%). The estimated vaccine efficacy for PHN incidence was 60.1% (-9.8%, 86.7%).The estimated vaccine efficacy for HZ pain BOI was 50.1% (14.1%, 71.0%).

The SPS Long-term Persistence Substudy (LTPS)

Following completion of the STPS, the open-label LTPS evaluated the duration of protection against HZ, PHN and HZ BOI of ZOSTAVAX on subjects vaccinated in the SPS. A total of 6,867 subjects previously vaccinated with ZOSTAVAX in the SPS participated in the LTPS. The mean age at enrollment into LTPS was 74.5 years.

Because placebo subjects were previously offered vaccine during the STPS, a concurrent placebo control group was not available for calculation of vaccine efficacy for the LTPS. Therefore, prior placebo recipients were used as a reference group for calculating vaccine efficacy in the LTPS.

The LTPS analyses for vaccine efficacy are based on data collected primarily from Year 7 through Year 10 following vaccination in the SPS. Median follow up during the LTPS was ~3.9 years (range is one week to 4.75 years). There were 263 evaluable HZ cases in 261 subjects (observed HZ incidence rate: 10.3 per 1000 Person-Years) during the LTPS. The estimated vaccine efficacy for HZ incidence during the LTPS follow-up period was 21.1% (10.9%, 30.4%). The estimated vaccine efficacy for PHN incidence was 35.4% (8.8%, 55.8%). The estimated vaccine efficacy for HZ BOI was 37.3% (26.7%, 46.4%).

INDICATIONS AND USAGE

ZOSTAVAX is indicated for:

- prevention of herpes zoster (shingles)

ZOSTAVAX is indicated for immunization of individuals 50 to 79 years of age.

ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY***).

CONTRAINDICATIONS

History of hypersensitivity to any component of the vaccine, including gelatin.

History of anaphylactic/anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin). Neomycin allergy generally manifests as a contact dermatitis. However, a history of contact dermatitis due to neomycin is not a contraindication to receiving live virus vaccines.

Primary and acquired immunodeficiency states due to conditions such as: acute and chronic leukemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS (see CLINICAL PHARMACOLOGY and SIDE EFFECTS); cellular immune deficiencies.

Immunosuppressive therapy (including high-dose corticosteroids); however, ZOSTAVAX is not contraindicated for use in individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or in patients who are receiving corticosteroids as replacement therapy, e.g., for adrenal insufficiency.

Active untreated tuberculosis.

Pregnancy (see **PREGNANCY**).

PRECAUTIONS

The health care provider should question the patient about reactions to a previous dose of any VZV-containing vaccines (see **CONTRAINDICATIONS**).

Serious adverse reactions, including anaphylaxis, have occurred with ZOSTAVAX.

As with any vaccine, adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic/anaphylactoid reaction occur.

Deferral of vaccination should be considered in the presence of fever >38.5°C (>101.3°F).

The safety and efficacy of ZOSTAVAX have not been established in adults who are known to be infected with human immunodeficiency virus (HIV) with or without evidence of immunosuppression. A phase II safety and immunogenicity study in HIV-infected adults with conserved immune function has been completed (see CLINICAL PHARMACOLOGY and SIDE EFFECTS).

As with any vaccine, vaccination with ZOSTAVAX may not result in protection of all vaccine recipients.

Transmission

In clinical trials with ZOSTAVAX, transmission of the vaccine virus has not been reported. However, post-marketing experience with varicella vaccines suggests that transmission of vaccine virus may occur rarely between vaccinees who develop a varicella-like rash and susceptible contacts. Transmission of vaccine virus from varicella vaccine recipients who do not develop a varicella-like rash has also been reported. This is a theoretical risk for vaccination with ZOSTAVAX. The risk of transmitting the attenuated vaccine virus to a susceptible individual should be weighed against the risk of developing natural zoster that could be transmitted to a susceptible individual.

PREGNANCY

Animal reproduction studies have not been conducted with ZOSTAVAX. It is also not known whether ZOSTAVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, naturally-occurring VZV infection is known to sometimes cause fetal harm. Therefore, ZOSTAVAX should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see **CONTRAINDICATIONS**).

NURSING MOTHERS

It is not known whether VZV is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if ZOSTAVAX is administered to a nursing woman.

PEDIATRIC USE

ZOSTAVAX is not recommended for use in this age group.

GERIATRIC USE

The mean age of subjects enrolled in the largest (N=38,546) clinical study of ZOSTAVAX was 69 years (range 59-99 years). Of the 19,270 subjects who received ZOSTAVAX, 10,378 were 60-69 years of age, 7,629 were 70-79 years of age, and 1,263 were 80 years of age or older. ZOSTAVAX was demonstrated to be generally safe and effective in this population.

ZOSTAVAX reduced the incidence of zoster by 64% (95% CI: [56 to 71%]) in individuals 60-69 years of age and by 41% (95% CI: [28 to 52%]) in individuals 70 to 79 years of age. The cumulative incidence of zoster over time among vaccine recipients was also significantly reduced ($p<0.001$; Figure 1).

DRUG INTERACTIONS

ZOSTAVAX must not be mixed with any other medicinal product in the same syringe. Other medicinal products must be given as separate injections and at different body sites.

Concurrent administration of ZOSTAVAX and antiviral medications known to be effective against VZV has not been evaluated.

ZOSTAVAX and PNEUMOVAX* 23 should not be given concomitantly because concomitant use resulted in reduced immunogenicity of ZOSTAVAX (see CLINICAL PHARMACOLOGY).

SIDE EFFECTS

In clinical trials, ZOSTAVAX has been evaluated for general safety in more than 32,000 adults 50 years of age or older. ZOSTAVAX was generally well tolerated.

ZOSTAVAX Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age
In the ZEST study, subjects received a single dose of either ZOSTAVAX (n=11,184) or placebo (n=11,212) and were monitored for safety throughout the study. During the study, a vaccine-related serious adverse experience was reported for 1 subject vaccinated with ZOSTAVAX (anaphylactic reaction).

All subjects received a vaccination report card (VRC) to record adverse events occurring from Days 1 to 42 postvaccination in addition to undergoing routine safety monitoring throughout the study.

The following very common (≥ 1/10) and common (≥ 1/100, <1/10) vaccine-related injection-site and systemic adverse experiences were reported in the ZEST study. Several adverse experiences were solicited (Days 1-5 postvaccination) and are designated with the * symbol.

Nervous system disorder
Common: headache

General disorders and administration site conditions

Very common: erythema,* pain,* swelling*, pruritus
Common: hematoma, warmth, induration

Musculoskeletal and connective tissue disorders
Common: pain in extremity

The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (63.9% for ZOSTAVAX and 14.4% for placebo).

Within the 42-day post vaccination reporting period in the ZEST, noninjection-site zosteriform rashes were reported by 34 subjects (19 for ZOSTAVAX and 15 for placebo). Of 24 specimens that were adequate for Polymerase Chain Reaction (PCR) testing, wild-type VZV was detected in 10 (3 for ZOSTAVAX, 7 for placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

Within the same 42-day postvaccination reporting period in the ZEST, varicella-like rashes were reported by 124 subjects (69 for ZOSTAVAX and 55 for placebo). Of 23 specimens that were available and adequate for PCR testing, VZV was detected in one of these specimens from the group of subjects who received ZOSTAVAX; however, the virus strain (wild type or Oka/Merck strain) could not be determined.

Shingles Prevention Study (SPS) in Subjects 60 Years of Age and Older
In the largest of these trials, the Shingles Prevention Study (SPS), 38,546 subjects received a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276) and were monitored for safety throughout the study. During the study, vaccine-related serious adverse experiences were reported for 2 subjects vaccinated with ZOSTAVAX (asthma exacerbation and polymyalgia rheumatica) and 3 subjects who received placebo (Goodpasture' s syndrome, anaphylactic reaction, and polymyalgia rheumatica).

In the Adverse Event Monitoring Substudy, a subgroup of individuals from the SPS (n=3,345 received ZOSTAVAX and n=3,271 received placebo) were provided vaccination report cards to record adverse events occurring from Days 0 to 42 postvaccination in addition to undergoing routine safety monitoring throughout the study.

The following very common (≥ 1/10) and common (≥ 1/100, <1/10) vaccine-related injection-site and systemic adverse experiences were reported in the Adverse Event Monitoring Substudy. Most of these adverse experiences were reported as mild in intensity. Several adverse experiences were solicited (Days 0-4 postvaccination) and are designated with the * symbol.

Nervous system disorder
Common: headache

General disorders and administration site conditions
Very common: erythema,* pain/tenderness,* swelling*
Common: hematoma, pruritus, warmth

The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (48% for ZOSTAVAX and 17% for placebo).

The remainder of subjects in the SPS received routine safety monitoring, but were not provided report cards. The types of events reported in these patients were generally similar to the subgroup of patients in the Adverse Event Monitoring Substudy.

Within the 42-day postvaccination reporting period in the SPS, the number of reported zosteriform rashes among all subjects was small (17 for ZOSTAVAX, 36 for placebo; p=0.009). Of these 53 zosteriform rashes, 41 had specimens that were available and adequate for PCR testing. Wild-type VZV was detected in 25 (5 for ZOSTAVAX, 20 for placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

Within the same 42-day postvaccination reporting period in the SPS, the number (n=59) of reported varicella-like rashes was also small. Of these varicella-like rashes, 10 had specimens that were available and adequate for PCR testing. VZV was not detected in any of these specimens.

Other Studies

In other clinical trials in support of the initial licensure of the frozen formulation of ZOSTAVAX, the reported rates of noninjection-site zosteriform and varicella-like rashes within 42 days postvaccination were also low in both zoster vaccine recipients and placebo recipients. Of 17 reported varicella-like rashes and non-injection site zoster-like rashes, 10 specimens were available and adequate for PCR testing, and 2 subjects had varicella (onset Day 8 and 17) confirmed to be Oka/Merck strain.

In clinical trials evaluating ZOSTAVAX in subjects 50 years of age or older, including a study of concomitantly administered inactivated influenza vaccine, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS. However, in these trials, a higher rate of injection-site adverse experiences of mild-to-moderate intensity was reported among subjects 50-59 years of age compared with subjects ≥ 60 years of age.

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 100 subjects 50 years of age or older with a history of herpes zoster (HZ) prior to vaccination to assess immunogenicity of ZOSTAVAX and the safety profile. In this clinical trial, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS.

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrollment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of ZOSTAVAX. All vaccinated study patients were followed for adverse experiences. Vaccine relatedness was determined by the investigator based upon blinded data. To evaluate the adverse experiences temporally associated with study vaccination, patients were given a Vaccination Report Card (VRC) to record any injection-site adverse experiences, systemic adverse experiences, elevated temperatures, and rashes from Days 1 to 42 postvaccination. Patients were followed for serious adverse experiences, regardless of whether the event was related to the study vaccine, throughout the course of the study (through Day 182 postvaccination). In this clinical trial, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS. (See **CONTRAINDICATIONS** regarding corticosteroids)

In a double-blind, placebo-controlled randomized clinical trial, ZOSTAVAX was administered as a two-dose regimen to human immunodeficiency virus (HIV)-infected adults (18 years of age or older) on potent combination antiretroviral therapy with conserved immune function (CD4+ T cell count ≥ 200 cells/μL). Although a two-dose regimen was used in this study, ZOSTAVAX is administered as a single dose regimen (See DOSAGE & ADMINISTRATION). In this clinical trial, a total of 295 subjects received dose 1 and 286 subjects received dose 2. All vaccinated study patients were followed for adverse experiences. Vaccine relatedness was determined by the investigator based upon blinded data. To evaluate the adverse experiences temporally associated with study vaccination, patients were given a Vaccination Report Card (VRC) to record any injection-site adverse experiences, systemic adverse experiences, elevated temperatures, and rashes through Week 6 following each vaccination. Patients were followed for serious adverse experiences, regardless of whether the event was related to the study vaccine, throughout the course of the study (through Week 24 following dose 1). In this clinical trial, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS. (See CONTRAINDICATIONS regarding immunosuppression due to HIV/AIDS.)

To address concerns for individuals with an unknown history of vaccination with ZOSTAVAX, the safety and tolerability of a second dose of ZOSTAVAX was evaluated. In a placebo-controlled, double-blind study, 98 adults 60 years of age or older received a second dose of ZOSTAVAX 42 days following the initial dose; the vaccine was generally well tolerated. The frequency of vaccine-related adverse experiences after the second dose of ZOSTAVAX was generally similar to that seen with the first dose.

Post-marketing Experience

The following additional adverse reactions have been identified during post-marketing use of ZOSTAVAX. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Gastrointestinal disorders: nausea

Infection and infestations: herpes zoster (vaccine strain)

Skin and subcutaneous tissue disorders: rash

Musculoskeletal and connective tissue disorders: arthralgia; myalgia

General disorders and administration site conditions: injection-site rash; injection-site urticaria; pyrexia; transient injection-site lymphadenopathy

Immune system disorders: hypersensitivity reactions including anaphylactic reactions.

OVERDOSAGE

There are no data with regard to overdose.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION.

Do not inject intravascularly.

Individuals should receive a single dose. At present, the duration of protection after vaccination with ZOSTAVAX is unknown. In the Shingles Prevention Study (SPS), protection was demonstrated through 4 years of follow-up. The need for revaccination has not yet been defined.

ZOSTAVAX is not a treatment for zoster or PHN.

ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine using separate syringes.

Reconstitute immediately upon removal from the refrigerator.

To reconstitute the vaccine, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine virus.

Vial of diluent:
To reconstitute the vaccine, first withdraw the entire contents of the diluent vial into a syringe. Inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of reconstituted vaccine subcutaneously, preferably into the upper arm (preferably in the deltoid region).

Prefilled syringe of diluent:
To reconstitute the vaccine, inject all the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of reconstituted vaccine subcutaneously, preferably into the upper arm (preferably in the deltoid region).

IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

Do not freeze reconstituted vaccine.

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of ZOSTAVAX because these substances may inactivate the vaccine virus.

A separate sterile needle and syringe should be used for administration of ZOSTAVAX to prevent transfer of infectious diseases.

Needles should be disposed of properly and should not be recapped.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ZOSTAVAX when reconstituted is a semi-hazy to translucent, off white to pale yellow liquid.

How Supplied

To be filled in locally.

STORAGE

Storage
During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 8°C (46°F) or colder.

ZOSTAVAX **SHOULD BE STORED REFRIGERATED** at a temperature of 2 to 8°C (36 to 46°F) or colder until it is reconstituted for injection (see **DOSAGE AND ADMINISTRATION**). The diluent should be stored separately at room temperature (20 to 25°C, 68 to 77°F) or in the refrigerator (2 to 8°C, 36 to 46°F).

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

DO NOT FREEZE THE RECONSTITUTED VACCINE.

Manufacturer: Merck Sharp & Dohme Corp.
Address: 770 Sumneytown Pike, West Point, PA 19486, U.S.A.
Manufacturer of diluent syringe：VETTER PHARMA-FERTIGUNG GMBH & CO. KG
Address: Schutzenstrasse 87, D-88212 Ravensburg, Germany
Manufacturer of diluent vial：Jubilant HollisterStier LLC (Small Volume Parenteral Facilities)
Address: 3525 North Regal Street, Spokane, WA 99207, U.S.A.
Packager：MERCK SHARP & DOHME B.V.
Address: Waarderweg 39, 2031 BN Haarlem, The Netherlands