.1 轉移性或無法手術切除且不適合局部治療或局部治療失敗之晚期肝細胞癌(HCC) 說明:本適應症之樞紐性試驗(試驗100554)所納入的試驗族群中,在以Child-Pugh評分,主要為Child-Pugh class A患者,,

數為Child-Pugh class B患者[參見臨床研究(14.1)]。 2.2 晚期腎細胞癌(RCC)且已接受interferon-alpha或interleukin-2治療失敗,或不適合以上兩種藥物治療之病患 3 放射性碘治療無效之局部晚期或轉移性的進行性(progi

Nexavar的每日建議劑量為一次400毫克(2颗200毫克錠劑),一天服用2次,不與食物一起服用(至少用餐前一小時或用餐後2,時)。口服使用,以水吞服。治療應持續直到病患無法再得到臨床效益或發生不可接受的毒性。 肝細胞癌及腎細胞癌的劑量調整方式

處理疑似藥物不良反應時,可能需要暫時中斷Nexavar治療及/或減少劑量。當必須要減少劑量時,Nexavar的劑量應降至每天 400毫克,若須進一步減少劑量,Nexavar的劑量可以降至每隔一天400毫克[參見警語和注意事項(6)]。 因皮膚毒性而劑量調整的建議如下表1所示

去1. 肝細胞或腎細胞症症患因皮膚素性的測器調整建議

表1:肝細胞或肾細胞癌病患因皮膚毒性的劑量調	登廷 礒	
皮膚毒性分級	發生	Nexavar劑量調整
第1級:麻木、感覺遲鈍、感覺異常、刺痛、無	任何時候	持續Nexavar治療並考慮局部治療以緩解症狀
痛腫大、紅斑或手或腳的不舒服感但不影響病		
患的日常活動		
第2級:疼痛的紅斑及手或腳的腫大及/或會影響	第一次發生	持續Nexavar治療並考慮局部治療以緩解症狀
病患日常活動的不舒服感		若七天內沒有改善,如以下方式處理
	若七天內沒有	中斷Nexavar治療,直到毒性改善到第0-1級
	改善或第二次	當回復治療時,減低Nexavar劑量至每天400毫克或每隔-
	或第三次發生	天400毫克
	第四次發生	停止Nexavar治療
第3級:濕性脫皮、潰瘍、皮膚水泡或手或腳的	第一次或第二	中斷Nexavar治療,直到毒性改善到第0-1級
嚴重疼痛、或嚴重的不舒服感導致病患無法工	次發生	當回復治療時,減低Nexavar劑量至每天400毫克或每隔-
作或日常生活作息		天400毫克
	第三次發生	停止Nexavar治療

分化型甲狀腺癌的劑量調整方式

Nexavar® film-coated tablets 200 mg

處理疑似藥物不良反應時,可能需要暫時中斷Nexavar治療及/或減少劑量。當治療分化型甲狀腺癌的過程中必須要減少劑量時, 劑量可以降至1錠200毫克,一天雨次,接續可再降至1錠200毫克,一天一次。當非血液學的不良反應獲得改善後,可以增加

责2:分化型甲狀腺癌病患之降低劑量建議

如果因出現皮膚毒性而必須降低劑量,請依照表3的建議降低NEXAVAR劑量。 3. 分化刑甲非晚瘟庄串用皮膚素从降低劑昌建議

皮膚毒性分級	發生	Nexavar劑量調整
第1級:麻木、感覺遲鈍、感覺異常、刺痛、手	任何時候	持續NEXAVAR治療
戊腳的無痛腫大、紅斑或不舒服感但不影響病		
患的日常活動		
第2級:疼痛的紅斑及手或腳的腫大及/或會影響	第1次發生	降低NEXAVAR的劑量至每天600 毫克
病患日常活動的不舒服感		若7天內沒有獲得改善,請參閱下方說明
	降低劑量後7	中斷使用NEXAVAR直到症狀解除或改善至第1級,如
	天內沒有改善	恢復使用NEXAVAR,須降低劑量(參見表2)
	或第2次發生	
	第3次發生	中斷使用NEXAVAR直到症狀解除或改善至第1級,如
		恢復使用NEXAVAR,須降低劑量(參見表2)
	第4次發生	永久停止使用NEXAVAR
第3級:濕性脫皮、潰瘍、皮膚水泡或手或腳的	第1次發生	中斷使用NEXAVAR直到症狀解除或改善至第1級,如
嚴重疼痛、或嚴重的不舒服感導致病患無法工		恢復使用NEXAVAR,須降低一個劑量層級(參見表2)
作或日常生活作息	第2次發生	中斷使用NEXAVAR直到症狀解除或改善至第1級,如:
		恢復使用NEXAVAR,須降低2個劑量層級(參見表2)
	第3次發生	永久停止使用NEXAVAR

自第2或第3級皮膚毒性恢復至第0-1級後,須降低NEXAVAR的治療劑量至少28天,接著也許可以將已降低的NEXAVAR劑 是高一個劑量層級。因皮膚毒性而需要降低劑量的病患,預期大約有50%可以達到上述可恢復較高劑量的標準,且恢復至 前劑量的病患,預期大約有50%可以耐受此劑較高劑量(即維持使用較高劑量且不會復發第2級或更嚴重的皮膚毒性) 不需根據病患年齡、性別或體重而調整劑量。

併用強效CYP3A4誘導劑:併用強效CYP3A4誘導劑會降低sorafenib血漿濃度,應避免使用(例如聖約翰草、dexamethasona phenytoin、 carbamazepine、rifampin、rifabutin、phenobarbital)。雖然目前未針對提高Nexavar劑量進行試驗,若必須併用強 CYP3A4誘導劑時,可考慮提高Nexavar劑量。若提高Nexavar劑量,應謹慎監控病患的毒性反應[參見藥物間交互作用(8.7)]

每錠含sorafenib tosylate (274 mg),相當於sorafenib 200 mg exavar藥錠為圓形、雙凸面的紅色膜衣錠,口服使用直徑10 mm、重量350 mg,雨面分別印有「Bayer十字標幟」和「200

Nexavar禁用於已知對sorafenib或其任何賦形劑有嚴重過敏的病患。 吏用carboplatin和paclitaxel治療鱗狀細胞肺癌病患時,禁止併用Nexavar [參見警語和注意事項(6.12)]。

6.1 心缺血及/或心肌梗塞的風險

在HCC試驗中,Nexavar組病患的心肌缺血/心肌梗塞發生率為2.7%,安慰劑組則為1.3%。而在RCC試驗1中,與治療相關的 心缺血或心肌梗塞的發生率,相較於安慰劑組(0.4%),在Nexavar組有較高的發生率(2.9%)。另於DTC試驗中,Nexavar組 患的心肌缺血/心肌梗塞餐生率為1.9%,安慰劑組則為0%。這個試驗排除有非穩定的冠狀動脈疾病或最近有心肌梗塞的: 患。心缺血及/或心肌梗塞病患须考慮暫時或永久停止使用Nexavar 6.2 QT間隔的延長

Vexavar顯示會延長QT/QTc的間隔(請見藥理學-藥效學),可能導致心室心律不整之風險增加。有或可能產生QTc延長之病患 應謹慎使用Nexavar,例如先天性長QT症狀的病患、以蔥環類藥物(anthracycline)之高蓄積劑量治療的病患、使用某些抗心律 不整藥物或其他造成QT延長之藥物的病患、和那些如低血鉀症、低血鈣症或低血鎂症之電解質不平衡的病患。當這些病患

吏用Nexavar時,應考慮定期監測治療中之心電圖和電解質(鎂、鉀、鈣) 6.3 出血的風險 服用Nexavar後可能發生出血危險性增加。在HCC試驗中,任何成因的出血過量均不明顯,Nexavar組病患食道靜脈曲張出血 七率為2.4%,安慰劑組病患為4%。Nexavar組病患因任何部位出血致死的通報比率為2.4%,安慰劑組病患則為4%。RCC試 儉1中發生的出血事件在Nexavar組為15.3%,安慰劑組為8.2%。出血事件報告為CTCAE第3及4級的發生率在Nexavar組分別

為2%及0%,而安慰劑組分別為1.3%及0.2%。RCC試驗1中的兩組各有一例致死的出血事件。DTC試驗中,通報出血事件的 比例,在NEXAVAR組為有174%,安慰劑組則為96%;不過CTCAE第3級出血的發生率在NEXAVAR組為1%,安慰劑組則↓ 久停止服用Nexavar。由於本藥物有出血風險,在給予DTC病患NEXAVAR前,應先以局部療法治療其氣管、支氣管及食 為47%;在兩組中均未觀察到CTCAE第3級和第4級的低白蛋白血症。 6.4 高血壓的風險

前六週Nexavar治療時須每週監測血壓,而後定期監測,必要時應依照標準醫療程序加以治療。在HCC試驗中,Nexavar治療 組病患發生高血壓的通報比率為9.4%,安慰劑組病患則為4.3%。RCC試驗1中指出,發生與治療相關的高血壓在Nexavar治 療組約為16.9%,安慰劑組為1.8%。DTC試驗中,通報高血壓的比例,在NEXAVAR組為40.6%,安慰劑組則為為12.4%。 高血壓通常為輕微至中度,在治療早期發生,可以使用標準抗高血壓藥物治療處理。發生嚴重或持續性高血壓,或在適當 的抗高血壓治療下仍有高血壓危象,則考慮永久停止服用Nexavar。在HCC試驗中,Nexavar組的297位病患中有1位因發生高 血壓而永久停藥,在RCC試驗1中,則為451位Nexavar治療病患中有1位因發生高血壓而永久停藥,另DTC試驗中,Nexavar

6.5 皮膚毒性的風險

Nexavar最常見的藥物不良反應是手足皮膚反應和出疹。出疹和手足皮膚反應通常屬於CTC (National Cancer Institute Common Toxicity Criteria美國國家癌症研究院通用毒性評分標準)第1和2級,且通常在Nexavar治療的首6週中開始出現。皮膚毒性的處 理可能包括症狀緩解的局部治療、暫時中斷Nexavar治療及/或調整劑量、對於嚴重或持續性的病例則可能要永久停止服用 lexavar。在297位Nexavar治療組HCC病患中有4位因發生手足皮膚反應而永久停止治療,451位Nexavar治療組RCC病患中則 有3位,另207位Nexavar治療組DTC病患中則有11(5.3%)位 曾有嚴重皮膚毒性的案例報告,包括史蒂芬強森症候群(Stevens-Johnson syndrome; SJS)及毒性表皮溶解症(toxic epiderma

ecrolysis; TEN)。這些案例有可能危及生命。如果懷疑是史蒂芬強森症候群或毒性表皮溶解症,則停用Nexavar。 腸胃道穿孔是不常見的,且不到1%服用Nexavar病患通報此事件。在有些案例這個事件明顯地與腹腔內腫瘤無關。若有腸胃

一些在Nexavar治療期間使用warfarin的病患曾報告不常見的出血事件或國際標準凝血時間比(International Normalized Rati INR)升高。定期監測同時使用warfarin病患的凝血酶原時間(Prothrombin time; PT)和INR的變化,以及應注意臨床上的出血事

目前尚未有關於Nexavar對傷口癒合影響的正式研究。對於接受大型外科手術的病患,建議暫時中斷Nexavar。關於大型手術後重新開始治療的時機,其臨床經驗有限,應以其傷口是否已適當癒合的臨床判斷為基準。

并用neomycin會造成sorafenib生體可用率降低[參見藥物間交互作用(8.5]。

6.10 胚胎傷害的風險 目前尚未有懷孕婦女使用Nexavar所進行適當且對照良好的試驗。然而,依據作用機轉和動物試驗的發現,懷孕婦女使用 Nexavar可能會造成胚胎的傷害。動物母體曝露在遠低於人類建議劑量(每天雨次400毫克)的Sorafenib下,會產生胚胎毒性。 由於對胚胎有潛在的危險,必須告知有生育能力的女性在接受Nexavar治療期間應避免受孕[參見特殊族群使用(9.1)]。

6.11 肝功能受損病患 肝功能受損可能會造成sorafenib的血漿濃度降低。比較不同試驗的數據顯示,HCC病患體內的sorafenib濃度低於非HCC病患

(無肝功能受捐)體內的sorafenib濃度。輕度(Child-Pugh A級)和中度(Child-Pugh B級)肝功能受損的HCC病患,其sorafenib的 AUC相似。目前未建立非HCC且肝功能受損病患的最理想劑量[參見特殊族群使用(9.7)和臨床藥理學(12.2)] <u>6.12 使用Carboplatin/Paclitaxel及Gemcitabine/Cisplatin治療鱗狀細胞肺癌病患時,併用Nexavar觀察到增加的死亡率</u> 在未曾接受過化學治療的IIIB-IV期非小細胞肺癌病患之2個隨機對照試驗中,其子集分析發現,與單獨使用carbopla

paclitaxel及單獨使用gemcitabine/cisplatin治療鱗狀細胞肺癌比較,併用NEXAVAR顯示有較高的死亡率【前者:HR 1.81, 95% CI 1.19-2.74)、後者:HR 1.22, 95% CI 0.82-1.80】。應禁止合併使用NEXAVAR和carboplatin/paclitaxel治療鱗狀細胞肺癌病患, 不建議合併使用NEXAVAR和gemcitabine/cisplatin治療鱗狀細胞肺癌病患,NEXAVAR使用於非小細胞肺癌病患的療效及安全 性尚未建立[參見不良反應(7.5)]

使用NEXAVAR治療分化型甲狀腺癌病患,建議密切監測血鈣數值,相較於腎細胞癌病患及肝細胞癌病患,低血鈣情形在分 化型甲狀腺癌病患的臨床試驗中較為頻繁及嚴重,特別是具有副甲狀腺功能減退病史的病患[參見不良反應(7.3)]。 6.14 减少分化型甲狀腺癌病患促甲狀腺荷爾蒙激素抑制的作用

NEXAVAR會減少外源性甲狀腺素的抑制作用。DTC試驗中,99%的病患其基線時的促甲狀腺荷爾蒙激素(TSH)濃度低於 0.5 mU/L。開始治療後觀察到NEXAVAR治療組,有41%其TSH高於0.5 mU/L,安慰劑治療組則為16%。NEXAVAR治療時發 生TSH抑制情形減少之病患,其TSH最大值的中位數為1.6 mU/L,而且這些病患中有25%其TSH濃度高於4.4 mU/L。

DTC病患須每月監測TSH濃度並視需要調整甲狀腺荷爾蒙素替代藥物 6.15 角質棘皮瘤(keratoacanthoma)及皮膚鱗狀細胞癌(skin squamous cell carcinoma

使用NEXAVAR有可能會出現角質棘皮瘤(keratoacanthoma)及皮膚鱗狀細胞癌(skin squamous cell carcinoma)。DTC試驗中。 NEXAVAR治療組有8例皮膚鱗狀細胞癌(7例來自試驗雙盲期;1例來自試驗開放期),而對照組則無,這8例產生皮膚鱗狀細 胞癌的患者皆在手術後恢復。臨床上應仔細觀察,發現異常時應接受皮膚科醫師診察,並做適當的處置。

下列嚴重不良反應在仿單的其它地方有較詳細的討論: 心肌缺血、心肌梗塞[參見警語與注意事項(6.1)]

·QT間隔的延長[參見警語與注意事項(6.2)及藥效學(12.3)]

•出血[參見警語與注意事項(6.3)] •高血壓[參見警語與注意事項(6.4)] •手足皮膚反應、皮疹、史蒂芬強森症候群及毒性表皮溶解症[參見警語與注意事項(6.5)]

•胃腸道穿孔[參見警語與注意事項(6.6)]

|·減少DTC病患的TSH抑制的作用[參見警語與注意事項(6.14)]

照試驗中,955位參與試驗的病患曝露於Nexavar的情形

此外,下列醫療上顯著的不良反應於臨床試驗中不常見:暫時性腦缺血發作、心律不整、血栓栓塞。這些不良反應與 avar的因果關係,尚未確立 於臨床試驗是在各種不同的狀況下進行,某項藥物臨床試驗所觀察的不良反應率,無法與其他藥物臨床試驗的不良反應 直接比較,亦不能反映實際臨床觀察到的不良反應率 1、7.2和7.3節中提出的資料,反映出針對肝細胞癌(n=297)、晚期腎細胞癌(n=451)或分化型甲狀腺癌(n=207)的安慰劑

.HCC、RCC或DTC病患中最常見且被認為與Nexavar相關的不良反應(≥20%)有:疲倦、感染、體重減輕、食慾減退、皮疹 F足皮膚反應、掉髮、腹瀉、噁心、胃腸道及腹部疼痛、高血壓和出血。 表4和表5顯示HCC病患發生的不良反應,表中為至少有10%病患通報且Nexavar治療組發生率高於安慰劑組的不良反應。有

6接受Nexavar治療的病患以及24%接受安慰劑治療的病患通報發生CTCAE第3級的不良反應。有6%接受Nexavar治療的病 以及8%接受安慰劑治療的病患通報發生CTCAE第4級的不良反應。 :至少有10%病患通報且Nexavar治療組發生率高於安慰劑組的不良反應-HCC試驗1(試驗100554) [參見臨床試驗(13)]

					, L	,	
	N	exavar ($N = 297$	7)	-5	妄慰劑(N = 302))	,
不良事件	所有等級	第3級	第4級	所有等級	第3級	第4級	
NCI-CTCAE v3	%	%	%	%	%	%	
分類/專業用語							
所有事件	98	39	6	96	24	8	
身體症狀							
疲倦	46	9	1	45	12	2	
體重減輕	30	2	0	10	1	0	
皮膚							•
皮疹/鱗狀脫皮	19	1	0	14	0	0	
掻癢	14	<1	0	11	<1	0	
手足皮膚反應	21	8	0	3	<1	0	
皮膚乾燥	10	0	0	6	0	0	
禿頭症	14	0	0	2	0	0	
胃腸道							
腹瀉	55	10	<1	25	2	0	
厭食症	29	3	0	18	3	<1	
噁心	24	1	0	20	3	0	
嘔吐	15	2	0	11	2	0	
便秘	14	0	0	10	0	0	
肝膽/胰臟							
肝功能異常	11	2	1	8	2	1	
疼痛							
疼痛,腹部	31	9	0	26	5	1	

6接受Nexavar治療的病患通報發生高血壓,安慰劑組則有4%。

4%接受Nexavar治療的病患通報發生CTCAE第3級高血壓,安慰劑組則有1%。兩治療組均無CTCAE第4級通報案例。18%接 ivar治療的病患通報發生出血,安慰劑组則有20%。在安慰劑組的CTCAE第3級和第4級出血比率均較高(CTCAE第3級 Nexavar組3%,安慰劑組5%; CTCAE第4級—Nexavar組2%,安慰劑組4%)。接受Nexavar治療病患通報發生食道靜脈曲張

< 1%接受Nexavar治療的病患通報發生腎衰竭,安慰劑組則為3%。不良反應(包括與疾病惡化相關的不良反應)在Nexavar治療

组及安慰劑组造成水久停藥的比率類似(Nexavar治療組為32%而安慰劑組為35%)。
表5:至少有10%病患通報且Nexavar治療組發生率高於安慰劑組的不良反應-HCC試驗2(試驗11849)[參見臨床研究(14)]

	N	exavar (N = 149))		安慰劑 (N = 75)	
NCI-CTCAE v3系統	所有等級	第3級	第4級	所有等級	第3級	第4級
器官分類/常用詞	%	%	%	%	%	%
所有不良反應	98	36	9	95	31	7
血液/骨髓						
血紅蛋白	20	4	4	15	0	0
白血球	11	1	0	8	4	0
血小板	22	4	2	13	1	0
心臟,全身性						
高血壓	22	3	0	5	1	0
身體症狀						
疲倦	34	5	0	20	4	0
發燒	26	2	0	11	3	0
體重減輕	42	3	0	17	1	0
皮膚						
禿頭症	27	0	0	1	0	0
手足皮膚反應	46	11	0	3	0	0
掻癢	12	0	0	12	1	0
皮疹/鱗狀脫皮	22	1	0	9	0	0
胃腸道						
厭食症	31	3	0	17	3	0
腹水	26	7	0	17	9	0
腹瀉	42	7	0	16	0	0
代謝/實驗室檢驗						
鹼性磷酸酶	26	4	0	19	1	0
丙胺酸轉胺酶(ALT)	32	5	1	24	7	0
天門冬胺酸轉胺酶(AST)	41	18	1	31	15	4
膽紅素	36	12	5	32	7	11
低白蛋白血症	22	0	0	21	0	0
低血鈉症	15	8	1	13	8	0
血磷酸鹽減少症	11	3	0	5	1	0
脂肪酶	13	2	0	5	0	0
疼痛						
疼痛,腹部-未細分	35	7	0	20	4	0
疼痛,背部	15	3	0	12	1	0
肺部/上呼吸道						
咳嗽	18	1	0	15	0	0

HCC病患實驗室檢驗異常(study 100554) 下列是在HCC病患所觀察到的實驗室檢驗異常:

件在Nexavar治療組有7%,而在安慰劑組則有6%。

實驗室檢驗中常發現低磷酸鹽血症,曾在35%接受Nexavar治療的病患中觀察到,安慰劑組則為11%;11%的Nexavar組病患發 TCAE第3級的低磷酸鹽血症(1-2 mg/dL),安慰劑組則為2%;曾有1例來自安慰劑組的CTCAE第4級低磷酸鹽血症(<1 mg/dL) 通報案例。低磷酸鹽血症的病因學以及其與Nexavar的相關性目前未明 曾在40%接受Nexavar治療的病患中觀察到脂肪酶升高,安慰劑組則為37%。兩組各有9%病患發生CTCAE第3級和第4級脂肪 曾在34%接受Nexavar治療的病患中觀察到澱粉酶升高,安慰劑組則為29%。兩組各有2%病患通報發生CTCAE第3級和第4級

297位接受Nexavar治療的病患中有1位通報發生臨床胰臟炎(CTCAE第2級) 為1.4%。無通報發生第4級出血症狀,而安慰劑組有一位出現致命性出血症狀。如果發生需要醫療介入的出血事件,應考慮 試驗中兩治療組的肝功能檢測值升高情形類似。曾在59%接受Nexavar治療的病患中觀察到低白蛋白血症,安慰劑組病患則 ur治療的病患中觀察到國際標準化凝血酶原時間比值(INR)升高,安慰劑組病患則為34%;4%接受

澱粉酶升高。多數脂肪酶和澱粉酶升高現象均為暫時性,且大部份的案例均未中斷Nexavar治療。

表6:至少有10%病患通報 B.Nexavar治療組發生率高於安慰劑組的不良反應-RCC試驗1(試驗11213)

exavar治療病患通報發生CTCAE第3級的INR升高,安慰劑組病患則為2%;兩組均無CTCAE第4級INR升高。 曾在47%接受Nexavar治療的病患中觀察到淋巴球減少,安慰劑組病患則為42% 曾在46%接受Nexavar治療的病患中觀察到血小板減少,安慰劑組病患則為41%;4%接受Nexavar治療病患通報發生CTCAI

第3或4級血小板減少,而安慰劑組病患少於1%。 表6記載在試驗11213中發生不良反應的RCC病患百分比,表中為至少10%病患通報且Nexavar治療組發生率高於安慰劑組的 不良反應。報告為CTCAE第3級的不良事件在Nexavar治療組有31%,而在安慰劑組則有22%。報告為CTCAE第4級的不良3

不良事件 NCI-CTCAE	N	exavar $(N = 45)$	1)	3	を慰劑 (N = 451)
v3	所有等級	第3級	第4級	所有等級	第3級	第4級
分類/專業用語	%	%	%	%	%	%
所有事件	95	31	7	86	22	6
心血管,全身性						
高血壓	17	3	< 1	2	< 1	0
體質性症狀						
疲倦	37	5	< 1	28	3	< 1
體重減輕	10	< 1	0	6	0	0
皮膚						
出疹/鱗狀脫皮	40	< 1	0	16	< 1	0
手足皮膚反應	30	6	0	7	0	0
掉髮	27	< 1	0	3	0	0
搔癢	19	< 1	0	6	0	0
皮膚乾燥	11	0	0	4	0	0
胃腸症狀						
腹瀉	43	2	0	13	< 1	0
噁心	23	< 1	0	19	< 1	0
食慾不振	16	< 1	0	13	1	0
區吐	16	< 1	0	12	1	0
便秘	15	< 1	0	11	< 1	0
出血						
出血-所有部位	15	2	0	8	1	< 1
神經						
感覺神經病變	13	< 1	0	6	< 1	0
疼痛						
疼痛 – 腹部	11	2	0	9	2	0
疼痛 - 關節	10	2	0	6	< 1	0
疼痛 – 頭痛	10	< 1	0	6	< 1	0
肺部						
4	1	2		1.0	•	. 4

不良事件(包括與疾病惡化相關的事件)造成永久停藥的比例在Nexavar治療組及安慰劑組是相近的(Nexavar治療組是10%而安

實驗室檢驗異常 '列是在RCC試驗1(試驗11213)中 RCC病患所觀察到的實驗室檢驗異常

實驗室檢查中常發現低磷酸鹽血症,觀察到Nexavar治療組有45%病患,相較於安慰劑組為11%病患有此現象。13%6 war組病患發生CTCAE第3級的低磷酸鹽血症(1-2 mg/dl),安慰劑組則為3%。Nexavar組或安慰劑組皆未報告有CTCAE第 4級的低磷酸鹽血症(< 1 mg/dl)。低磷酸鹽血症的病因學與Nexavar的相關性尚未知。

的Nexavar组病患發生脂肪酶升高,相較於安慰劑組為30%。有12%的Nexavar组病患發生CTCAE第3或4級的脂肪酶升 高,相較於安慰劑組為7%。30%的Nexavar組病患發生澱粉酶升高,相較於安慰劑組為23%。有1%的Nexavar組病患報告有 CTCAE第3或4級的澱粉酶升高,相較於安慰劑組為3%。很多脂肪酶和澱粉酶值升高都是短暫的且大部份的案例都沒有中斷 xavar治療。451名Nexavar治療組病患中有3人報告臨床胰臟炎(1個CTCAE第2級和2個CTCAE第4級),而451名安慰劑組病 患中則有1人(CTCAE第2級)

23%的Nexavar组病患發現淋巴球減少,相較於安慰劑組為13%,CTCAE第3或第4級的淋巴球減少在Nexavar組病患報告有 13%,安慰劑組則為7%。嗜中性白血球減少在Nexavar組病患報告有18%,安慰劑組則為10%,CTCAE第3或第4級的嗜中性 白血球減少在Nexavar組病患報告有5%,安慰劑組則為2%。 貧血在Nexavar組病患報告有44%,安慰劑組則為49%,CTCAE第3或第4級的貧血在Nexavar組病患報告有2%,安慰劑組則

血小板減少在Nexavar組病患報告有12%,安慰劑組則為5%,CTCAE第3或第4級的血小板減少在Nexavar組病患報告有1% 安慰劑組則無。 7.3 DTC試驗中的不良反應

lexavar的安全性藉由一項雙盲試驗,評估416位病患具局部復發或轉移、進行性且放射性碘治療無效的分化型甲狀腺癌, 这些病患經隨機分配接受每天兩次400毫克Nexavar (n=207)或安慰劑組(n=209),直到疾病惡化或出現無法接受的毒性為止 [參見臨床試驗(14.3)]。下述資料反映Nexavar暴露期中位數46週(範圍為0.3至135週)。接受Nexavar治療的族群中有50%為男 13. 臨床前安全性資料 Sorafenib抑制CYP2B6及CYP2C8的Ki值分別為6及1-2μM。在一個單獨的臨床試驗中,併用Nexavar和paclitaxel導致經 13.1 致癌性,致突變性,生育力損分

應而導致治療中止的病患為14%,安慰劑組則為1.4%。 表7為DTC試驗於雙盲階段中,DTC病患接受Nexavar治療組發生不良反應比例高於安慰劑組之不良反應的百分比。Nexavar 1有53%發生CTCAE第3級不良反應,安慰劑組則為23%;接受Nexavar組有12%發生TCAE第4級不良反應,安慰劑組患則為

:病患發生特定不良反應的比例,Nexavar組具較高的發生率[組間差異≥5%(所有等級)1或≥2%(第3和第4級)]

MedDRA主要系統器官分類 &		AR (N= 207)		(N=209)
常用詞	所有等級(%)	第3和第4級(%)	所有等級(%)	第3和第4級(%)
Gastrointestinal disorders 胃腸消化系統異常				
腹瀉	68	6	15	1
噁心	21	0	12	0
腹部疼痛2	20	1	7	1
便秘	16	0	8	0.5
口腔炎3	24	2	3	0
嘔吐	11	0.5	6	0
口腔疼痛4	14	0	3	0
全身性異常與投藥部位狀況				
疲倦	41	5	20	1
全身無力	12	0	7	0
發燒	11	1	5	0
檢查				
體重減輕	49	6	14	1
代謝與營養異常				
食慾降低	30	2	5	0
肌肉骨骼與結締組織異常				
四肢疼痛	15	1	7	0
肌肉痙攣	10	0	3	0
良性、惡性與性質不明的腫瘤				
皮膚鱗狀細胞癌	3	3	0	0
神經系統異常				
頭痛	17	0	6	0
味覺異常	6	0	0	0
呼吸道、胸部與縱膈異常				
發生困難	13	0.5	3	0
鼻出血	7	0	1	0
皮膚與皮下組織異常				
PPES ⁵	69	19	8	0
掉髮	67	0	8	0
紅疹	35	5	7	0
掻癢	20	0.5	11	0
皮膚乾燥	13	0.5	5	0
紅斑	10	0	0.5	0
過度角化症	7	0	0	0
血管異常				
高血壓6	41	10	12	2

4 包括下列用詞:口腔疼痛、口咽不適、舌炎、灼口症候群、舌痛 5 肢端紅腫症(手足皮膚反應) 6 包括下列用詞:高血壓、血壓上升、收縮壓上升

本仿單中討論了TSH濃度升高的相關資訊/參見警辞與注意事項(6.14)]。相較於安慰劑組,Nexavar組DTC病患有觀察到下列 的實驗室檢查異常,在RCC和HCC試驗中也觀察到類似現象:脂肪酶、澱粉酶、低鉀血、低磷酸血、嗜中性白血球減少、 淋巴球減少、貧血以及血小板減少[參見不良反應(7.1、7.2 分別有59%及54%的Nexavar組病患發現血清ALT及AST升高,而安慰劑組則分別為24%及15%,其中高程度(>3級)的ALT及 ST上升,在Nexavar組病患分別為4%及2%,而於安慰劑組為無。

相較於RCC或HCC的病患,DTC病患有較高頻率及較嚴重的低血鈣發生,特別是在那些具有副甲狀腺功能減退病史的患者。 有36%的Nexavar治療組的DTC病患發生低血鈣情形(Grade 3以上有10%),而安慰劑組為11%(Grade 3以上有3%)。在DTC試 驗中,血清鈣的數值為每個月監測。 7.4 從多個臨床試驗或上市後使用所獲得的資訊

最重要的嚴重不良反應為心肌梗塞/心肌缺氧、胃腸穿孔、藥物誘發性肝炎、出血和高血壓/高血壓危象。最常見的不良反應 **9.4生育** 為腹瀉、疲倦、皮疹、秃髮、感染以及手足皮膚反應(相對應於MedDRA的肢端紅腫症 在多個臨床試驗或上市後經驗所通報的不良反應依照系統器官分類(in MeDRA)及發生頻率表示在下表8

| 發生頻率定義為:非常常見(≥ 1/10), 常見≥ 1/100 to < 1/10),, 不常見(≥ 1/1,000 to < 1/100), 罕見(≥ 1/10,000 to < 1/1,000)以及未 在每個發生頻率的組別,不良反應依嚴重程度遞減呈現。

系統器官分類	非常常見	常見	不常見	罕見	未知
	≥ 1/10	≥ 1/100 to < 1/10	≥ 1/1,000 to < 1/100	$\geq 1/10,000 \text{ to} < 1/1000$	
感染和寄生蟲感染	感染	毛囊炎			
血液和淋巴系統失調	淋巴球減少	白血球減少、嗜中性白			
		血球減少、貧血、血小			
		板減少			
免疫系統失調			過敏性休克反應過敏性反		血管性血腫
			應(包括皮膚反應和蕁麻		
			疹)		
內分泌失調		甲狀腺機能減退	甲狀腺機能亢進		
代謝及營養失調	食慾減退	低血鈣	脫水		
	低磷酸鹽血症	低血鉀			
		低血鈉症			
精神狀態失調		憂鬱症			
神經系統失調		週邊感覺神經病變、味	可逆性後腦白質病變*		
		覺改變			
耳朵和內耳失調		耳鳴			
心臟功能失調		鬱血性心衰竭*		QT延長	
		心肌缺血且/或心肌梗			
		塞*			
血管功能失調	出血(包括腸胃道*、呼	潮紅	高血壓危象*		
	吸道*及腦出血*)、高				
	血壓				
呼吸道、喉部及縱膈失		發聲困難	類間質性肺炎事件*[放射		
調		流鼻水	線性肺炎、急性呼吸窘迫		
			、間質性肺炎、肺部發炎		
			(pneumonitis, pulmonitis		
			and lung inflammation)等]		
胃腸道失調	腹瀉、噁心、嘔吐、便	口腔炎(包括口乾和舌	胰臟炎、胃炎、腸胃道穿		
	秘	痛)、消化不良、吞嚥	孔*		
		困難、胃食道逆流症			
肝膽系統失調			膽紅素升高及黃疸、膽囊	藥物誘發生肝炎*	
			炎、膽管炎		
皮膚及皮下組織失調	皮膚乾燥、皮疹、禿髮	角質棘皮瘤/皮膚鱗狀	濕疹、多形性紅斑		毒性表皮壞死溶解症
	、手足皮膚反應**	細胞癌、剥落性皮膚炎			放射線回憶性皮膚
	掻癢、紅斑	、面皰、皮膚脫屑、角			(radiation rec
		化過度症			dermatitis)、白細胞
					碎性血管
					(leukocytoclas
	I	l		I	11.11 \ L 45 45 3

	ΙI				、間質性肺炎、肺部發炎		
	ш				(pneumonitis, pulmonitis		
٩E	ш				and lung inflammation)等]		
	ш	胃腸道失調	腹瀉、噁心、嘔吐、便	口腔炎(包括口乾和舌	胰臟炎、胃炎、腸胃道穿		
	ш		私	痛)、消化不良、吞嚥	孔*		
的	ш			困難、胃食道逆流症			
事	ш	肝膽系統失調			膽紅素升高及黃疸、膽囊	藥物誘發生肝炎*	
	ш				炎、膽管炎		
	ш	皮膚及皮下組織失調	皮膚乾燥、皮疹、禿髪	角質棘皮瘤/皮膚鱗狀	濕疹、多形性紅斑		毒性表皮壞死
_	ш		、手足皮膚反應**	細胞癌、剝落性皮膚炎			放射線回憶
	ш		握癢、紅斑	、面皰、皮膚脫屑、角			(radiation
\dashv	ш			化過度症			dermatitis) \
	ш						碎性血
	ш						(leukocyto
	ш						vasculitis)、史
	ш						症候群
	ш	肌肉骨骼、結締組織及	關節痛	肌肉痛			横紋肌溶解症
	ш	骨骼失調		肌肉痙攣			
	ш	腎臟和泌尿系統的失調		腎衰竭、蛋白尿		腎病症候群	
	ш	生殖系統和乳房異常		勃起功能障礙	男性女乳症		
	ш	全身性失調及投與部位	疲倦、疼痛(包括嘴痛	無力衰弱、類流感之不			
	ш	狀況	、腹痛、骨頭痛、腫瘤	適、黏膜發炎			
	H		痛、頭痛)、發燒				
	ΙI	實驗室檢查	脂肪酶升高、澱粉酶升	轉胺酶短暫性升高	鹼性磷酸酶短暫性升高、		
- 1	ΙI		方 聯本 少 細		DID 法用选、权力数据法		

這些不良反應可能會造成威脅生命或致命的結果。這些事件是不常見或較不常見

在雨項隨機分配對照試驗中,比較sorafenib併用兩個platinum-based化療製劑(carboplatin/paclitaxel及另外的gem latin)以及單用兩個platinum-based化療製劑作為晚期非小細胞肺癌(NSCLC)患者第一線治療的安全性及療效,未達預期故 善整體存活期的主要療效指標。發生的安全性事件主要都和之前通報過的一致。然而在這兩個試驗中在鱗狀細胞肺癌病患 次族群中,都曾觀察到接受sorafenib併用兩個platinum-based化療製劑者死亡率較只接受兩個platinum-based化療製劑者為高)現象(paclitaxel/carboplatin:風險比[HR] 1.81,95%信賴區間[CI] 1.19-2.74; gemcitabine/cisplatin:風險比[HR] 1.22,95%信賴 [問[CI] 0.82 – 1.80)。並未確認其原因為何

相較於腎性胞癌病患或肝細胞癌病患的試驗,某些藥物不良反應在分化型甲狀腺癌病患的臨床試驗中有實質較高的發生頻 ,例如手足皮膚反應、腹瀉、禿髮、體重減輕、高血壓、低血鈣、角質棘皮瘤/皮膚鱗狀細胞癌。

8.1 UGT1A1和UGT1A9受力 xavar與主要經由UGT1A1路徑代謝/排泄的化合物(如irinotecan)併用時應小心。體外資料顯示sorafenib經由UGT1A1 (Ki值 μM)和UGT1A9 (Ki值2 μM)路徑抑制醛糖酸作用。Nexavar併用irinotecan時,其活性代謝物SN-38進一步經由UGT1A1路徑 弋謝,使SN-38的AUC增加67-120%。與Nexavar併用時,UGT1A1和UGT1A9的受質全身性曝露量可能會增加。

Vexavar (一天二次200或400 mg於21天週期的第2到19天給與) 與Docetaxel (每21天給與75或100 mg/m²) 併用時,三天的停藥 期間,docetaxel的AUC增加36-80%,C_{max}增加16-32%。建議當Nexavar與docetaxel併用時要謹慎進行 8.3 Doxorubicin/Irinotecan 同時使用Nexavar治療使doxorubicin的AUC增加21%。雖然這些發現的臨床意義未明但Doxorubicin與Nexavar併用時應小心。

;併用irinotecan時,其活性代謝物SN-38進一步經由UGT1A1路徑代謝,使SN-38的AUC增加67 120%,而irinotecan的AUC增 m26-42%。這些試驗結果的臨床意義尚不清楚。 xavar與fluorouracil併用時,曾觀察到fluorouracil的AUC升高(21%至47%)或降低(10%)。Fluorouracil/leucovorin與Nexavar併

用時應小心。 并用neomycin這類用於消滅腸胃道菌相的非全身性抗生素藥物,會干擾sorafenib肝腸再循環[參見臨床藥理學,代謝與清除], 造成sorafenib曝露量降低。健康自願受試者接受5日neomycin治療,其sorafenib平均生體可用率降低54%。這些發現的臨床意 義未明。尚未針對其他抗生素的影響進行試驗,但有可能與抗生素降低葡萄糖醛酸酶活性的能力有關。

CYP2C8形成之paclitaxel活性代謝物6-OH paclitaxel的曝露量無減少反而增加。這些數據暗示sorafenib可能不是CYP2C8的體 未曾對sorafenib進行致癌性研究

8.7 CYP3A4誘導物 持續併用Nexavar和rifampicin會導致sorafenib的AUC平均減少37%。其他CYP3A4活性誘導劑(例如學名為Hypericum perford 的聖約翰草、phenytoin、carbamazepine、phenobarbital和dexamethasone)也會增加sorafenib代謝,因而減少sorafenib濃度 [參見劑量與使用方法(3)] 8.8 CYP3A4抑制劑和CYP同質異構酵素受質

體外試驗資料顯示sorafenib經由CYP3A4及UGT1A9路徑代謝。健康自願者每天服用ketoconazole 400毫克(強的CYP3A4抑制 劑)一次,連續7天時,並未改變單一劑量50毫克.sorafenib的平均AUC。因此,sorafenib與CYP3A4抑制劑不太可能會有臨床

人類肝臟微粒體的試驗顯示sorafenib是CYP2C19、CYP2D6及CYP3A4的競爭性抑制劑,其Ki值分別為17 μM, 22 μM及29 μM 臨床上Nexavar併用midazolam,dextromethorphan和omeprazole (分別為CYP3A4、CYP2D6和CYP2C19之受質),4週後並無影 響這些藥物的曝露量。這表示sorafenib既不是這些CYP450同質酵素的抑制劑也非誘導物。

服用Nexavar 400毫克每天雨次連續28天,並不會改變併服的midazolam (CYP3A4受質)、dextromethorphan (CYP2D6受質). eprazole (CYP2C19受質)的曝露量,這表示sorafenib不太可能會改變這些酵素受質於體內的代謝 人類肝臟微粒體的研究顯示sorafenib是CYP2C9的競爭性抑制劑,其Ki值為7-8μM。

enib對CYP2C9受質warfarin代謝的可能影響已間接地以檢查PT-INR的方式評估。相對於安慰劑,服用Nexavar病患, PT-INR相對於基準的平均變化並未較高,推測於體內sorafenib並不會抑制warfarin的代謝,且可能不是CYP2C9的體內抑制劑。 [參見警語和注意事項(6.7)]

8.9 體外試驗: CYP酵素誘導 體外培養的人類肝臟細胞以sorafenib處理後不改變CYP1A2及CYP3A4的活性,顯示sorafenib不太可能是CYP1A2及CYP3A 持續併用Nexavar和rifampicin導致sorafenib AUC平均降低37%。其他CYP3A4活性的誘導物(如Hypericum perforatum又名聖約

8.10 合併其他抗癌藥物 臨床試驗中,Nexavar已和其他多種抗癌藥物,包括gemcitabine、cisplatin、oxaliplatin、paclitaxel、carboplatin、capecitabine、doxorubicin、docetaxel、irinotecan以及cyclophosphamide,以其常用的劑量組合合併使用。Nexavar對gemcitabine、cisplatin、

carboplatin、oxaliplatin或cyclophosphamide的藥動性質沒有臨床上顯著的影響。 8.11 Paclitaxel/Carboplatin 併用paclitaxel (225 mg/m²)和carboplatin (AUC=6)及Nexavar (100、200或400 mg每日雨次),服用Nexavar與paclitaxel/carboplatin 之間有3天停藥間隔時,對paclitaxel藥動性質並無顯著影響。有關irinotecan、docetaxel、doxorubicin和fluorouracil/leucovorin (HR:0.58, p=0.000007)(參見表10)

併用paclitaxel (225 mg/m², 每3週一次)和carboplatin (AUC = 6)及Nexavar (400 mg每日雨次, 無停藥間隔), 導致sorafenib的曝 霉量增加47%,paclitaxel的曝露量增加29%及6-OH paclitaxel的曝露量增加50%。對carboplatin的藥動性質並無影響。 這些資料表示當併用paclitaxel、carboplatin及Nexavar服用之間有3天停藥間隔時無須調整劑量。併用Nexavar無停藥間隔而使 enib和paclitaxel的曝露量增加之臨床意義未知 8.12 Capecitabine

併用capecitabine (750-1050 mg/m^2 毎日兩次,每21天的第1到14天)和Nexavar (200或400 mg毎日兩次,持續無間斷給與),導致 afenib的曝露量無顯著變化,但capecitabine的曝露量增加15-50%及5-FU的曝露量增加0-52%。當併用Nexavar時, pecitabine和5-FU的曝露量小至中幅度增加之臨床意義未知。

懷孕分類D [參見警語和注意事項(6 10)]

翰草、phenytoin、carbamazepine、phenobarbital和dex

依據作用機轉和動物試驗的發現,懷孕婦女使用Nexavar可能會造成胚胎的傷害。動物母體曝露在遠低於人類建議劑量(每天 两次400毫克)的Sorafenib下,會產生胚胎毒性。目前尚未有懷孕婦女使用Nexavar所進行適當且對照良好的試驗。告知有生 育能力的女性,Nexavar會造成出生缺陷或流產。指導有生育能力的男性及女性患者在使用Nexavar治療的期間及停止治療後 至少兩個星期,應該使用有效的避孕措施。如果女性患者在服用Nexavar的期間懷孕,建議聯繫醫師。 於大鼠及兔子器官形成的期間,Sorafenib有致畸胎性及引起胚胎毒性(包括增加著床後流產、再吸收、骨性遲緩及胎兒體重 遲緩。這些結果認為是發生在遠比人類建議劑量(每天兩次400毫克)(以體表面積來看大約是500 mg/m²/day)更低的劑量。給 予大鼠劑量大於0.2 mg/kg/day (1.2 mg/m²/day)及兔子劑量大於0.3 mg/kg/day (3.6 mg/m²/day),觀察到子宮內發育的不良影響。這個劑量下的藥物曝露(AUC)相當於人類建議使用劑量下AUC的0.008倍。沒有一個物種建立無明顯有害效應劑量 AEL),因為並未測試更低的劑量

9.2 有懷孕可能的女性 在動物實驗中,sorafenib已經顯示具有致畸性及胚胎毒性。在治療期間以及完成治療後至少兩周應該使用適當的避孕措施。 參見警語和注意事項及臨床前安全性資料)

目前未知sorafenib是否會分泌至人類乳汁中。在動物實驗中,sorafenib和/或代謝物會分泌至乳汁。 由於許多藥物會分泌至人類乳汁中,以及Nexavar對哺乳中嬰兒的潛在嚴重不良反應,應在考量藥物對母親的重要性後, Nexavar治療期間是否停止餵哺母乳或停藥 以幅射標幟的sorafenib施予授乳的Wistar大鼠,約有27%放射性會分泌至乳汁中。乳汁與血漿曲線下面積的比例約為5:1

在動物實驗中指出sorafenib會損傷男性及女性的生育能力(參見臨床前安全性資料)。

9.5 兒科使用 Nexavar對於兒科病患的安全性與有效性尚未建立。

對成長中的幼犬重覆給予sorafenib每日劑量≥600 mg/m²/day (相當於人類建議劑量時的AUC的0.3倍)時,股骨生長板不規則增厚;200 mg/m²/day (相當於人類建議劑量時的AUC的0.1倍)時,鄰接生長板有改變的骨髓發生細胞過少;及600 mg/m²/day ,牙齒象牙質的組成改變。當劑量持續四週或更短時,成大則並未有類似的影響 9.6 老年人使用 總計接受Nexavar治療的HCC病患中,年齡65歲或以上有59%,年齡75歲和以上有19%。而以Nexavar治療的RCC病患65歲或

病患間並沒有不同的反應,但不能排除有些老年人有較高的感受性。 9.7 肝功能受損病患 一項試驗觀察到輕度肝功能受損(Child-Pugh A)或中度肝功能受損(Child-Pugh B)的HCC患者,其sorafenib全身曝露量(AUC)介 於無肝功能損傷病患全身曝露量的範圍內。在另一項針對非HCC患者的試驗中,輕度肝功能受損(n=15)或中度肝功能受損(n=14)其全身曝露量相似於肝功能正常的患者(n=15)。對於輕度或中度肝功能受損的患者,毋須調整劑量。目前尚未研究

以上的有32%,75歲和以上的有4%。安全或療效方面在老年或年輕病患間並沒有不同,其他報告的臨床經驗在老年或年輕

fenib在嚴重肝功能受損(Child-Pugh C)患者體內的藥物動力學[參見藥物動力學(12.2)]。 9.8 腎功能受損病患 比較腎功能正常患者和輕度(CrCl 50-80 mL/min)、中度(CrCl 30-<50 mL/min或嚴重腎功能受損(CrCl <30 mL/min)但未接受透析治療的病患口服單一劑量400毫克的Nexavar,沒有觀察到sorafenib曝露量和腎功能的關聯性。有輕度、中度或嚴重腎功能受損但未接受透析治療的病患,於服用Nexavar時不需調整劑量。目前尚未針對透析病患,執行sorafenib的藥物動力學試驗

建議監測具腎功能障礙風險病患之體液平衡及電解質。

lexavar藥物過量沒有特別的治療

臨床試驗中Nexavar最高劑量為每次800毫克,每天2次。此劑量下觀察到的不良反應主要是腹瀉和皮膚事件。因為在動物的 口服急性毒性試驗中藥物的飽和吸收,並未有動物急性過量症狀的相關資料。 若懷疑有藥物過量的情形,應停止服用Nexavar並給予支持性治療

Nexavar膜衣錠200毫克是一種激酶抑制劑(kinase inhibitor),主成分是sorafenib的甲苯磺酸(tosylate)鹽類 Sorafenib tosylate的化學名為4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]-ureido}phenoxy)-N²-methylpyridine-2-carboxamic 4-methylbenzenesulfonate.而結構式為

rafenib tosylate是白色到淡黄或淡褐色固體,分子式為C₂₁H₁₆ClF₃N₄O₃ x C₇H₈O₃S,分子量為637.0 g/mole. Sorafenib tosylate∮

每一個紅色圓形的Nexavar膜衣錠含274毫克sorafenib tosylate相當於200毫克sorafenib 賦形劑含: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, magnesium stearate, macrogol 335 itanium dioxide及ferric oxide red

腫瘤細胞的訊息傳遞、血管增生和細胞凋亡有關。Sorafenib抑制人類肝細胞癌、腎細胞癌的腫瘤生長及血管增生,在免疫功能缺損小鼠中數種人類腫瘤異體移植的模式上也觀察到相同效果。Sorafenib亦抑制分化型甲狀腺癌的腫瘤生長。 療效分析結果顯示Ne

12.2 藥物動力學 投與Nexavar錠劑後,與口服溶液比較,其平均相對生體可用率為38-49%。Sorafenib的清除半衰期約為25-48小時。多次投與 表12:HCC試驗2(試驗11849)的療效結果 sorafenib連續7天後所造成的累積量為單次投藥的2.5到7倍。Sorafenib血漿濃度在7天內達到穩定狀態,平均濃度的峰谷值比小療效參數 評估DTC、RCC和HCC病患投與Nexavar 400 mg一天2次後的Sorafenib穩定狀態濃度,DTC病患的平均穩定狀態濃度為HCC病患的1.8倍和RCC病患的2.3倍,DTC病患其Sorafenib濃度增加的原因仍不清楚。

口服投與後, sorafenib約在3小時達到最高值血漿濃度。當與含中度脂肪餐食(30%脂肪;熱量700卡)服用時,生體可用率與空 [中位數,日數(95% CI)] 腹時相似。如果與高脂肪餐食(50%脂肪;熱量900卡)服用,sorafenib的生體可用率會比空腹時減少29%。建議Nexavar不與食 物一起服用[參見劑量與使用方法(3)]。

口服投與劑量超過400毫克每天2次時,平均Cmax和AUC的上升低於正比關係。

體外試驗中sorafenib與人類血漿蛋白的結合率為99.5%。

胃腸道的細菌葡萄糖醛酸酶活性分解,進行未共軛化藥物的再吸收作用。與neomycin併用會干擾此過程,降低54%的sorafenib 在穩定狀態時約有70-85%的sorafenib分解物在血漿中循環。已確認的sorafenib代謝物有8個,其中有5個在血漿中發現。 sorafenib主要的代謝物(pyridine N-oxide)於體外試驗中發現其與sorafenib有相似的效價,而約佔穩定狀態時循環分解物的9-16%。 r服100mg sorafenib溶液後,14天時有96%劑量的回收,77%於糞便中排除,19%於尿液中以醛糖酸化後的代謝物排除。約有 51%為未代謝的sorafenib於糞便中發現,但未於尿液中發現。 年齡、性別及種族的影響:一項sorafenib的藥動學試驗顯示,亞洲人(n = 78) sorafenib的平均AUC較西方人(n = 40)低30%,性

沒有兒科病患的藥物動力學資料

別和年齡對sorafenib的藥動學沒有臨床上有意義的影響。

orafenib主要經由肝臟清除。在輕度肝功能受損(Child-Pugh A級)或中度肝功能受損(Child-Pugh B級)的肝細胞癌病患其藥物曝 霉量範圍和沒有肝功能受損的病患相似。Sorafenib的藥物動力學在非肝細胞癌的Child-Pugh A級及Child-Pugh B級肝功能受損 病患和健康的自願者相似 目前尚未針對重度(Child-Pugh C級)肝功能受損病患進行sorafenib的藥物動力學試驗[參見警語和注意事項(6.11)和特殊族群使用

在健康受試者口服單次劑量輻射標幟sorafenib的藥物清除試驗中,有19% sorafenib劑量從尿液中排除。 生一項臨床藥理學試驗中,評估腎功能正常、輕度腎功能受損(CrCl > 50-80 ml/min)、中度腎功能受損(CrCl 30-50 ml/min)或嚴 重腎功能受損(CrCl < 30 ml/min)且未進行透析的受試者,服用單次400 mg劑量後的sorafenib藥動性質。未觀察到sorafenib曝露 量和腎功能之間的關係。有輕度、中度或嚴重腎功能受損但未進行透析的病患,不需調整劑量[參見特殊族群使用(9.8)]。

E一個臨床藥理學試驗中,記錄31位病患於基準線(治療前)與治療後之QT/QTc測量值。在一個28天治療週期後,與安慰劑组 於基準線相比較,sorafemib達到最高濃度時,QTcB延長了 4 ± 19 msec,QTcF則延長了 9 ± 18 msec。治療後之心電圖監測沒有病患顯示QTcB或QTcF大於500 msec [參見特殊警語和使用注意事項]。

&AUC的比較),會有輕微到中度改變(退化和新生)。給予未成年及發育中的狗重覆劑量後,在低於臨床曝露值下,觀察到畫 骨頭和牙齒的影響。其變化包括在股骨的生長板有不規則的增厚,鄰近被改變生長板旁的骨髓細胞不足,以及改變了象牙質 的組成。成年的狗沒有相類似的影響。 E一項體外哺乳類細胞(中國倉鼠卵巢)研究中,在代謝活化的狀態下具有致染色體變異性(染色體變異)而得到sorafenib的基因

毒性陽性反應。在一項體外細菌細胞研究(Ames測試)中sorafenib沒有基因毒性或在一項體內鼠微細胞核研究中顯示sorafenib沒 改染色體變異性。製程中的一個中間產物,在最終主成分中也有少許存在(< 0.15%),單獨的體外細菌細胞研究(Ames测試)中, 它顯示致基因突變性。

6未有專門的動物試驗評估sorafenib對生育力的影響。然而,可以預期對雄性及雌性的生育力有不良影響,因為在動物的重 覆剂量毒性试验颠示对於雄性和雌性生殖器官有改變。大鼠的典型變化包括睪丸、副睪丸、前列腺及精囊萎缩或退化。雌 t大鼠觀察到黃體的中心性壞死及卵巢濾泡的停止發展。狗在劑量600 mg/m²/day觀察到睪丸曲細精管的退化而在Sorafeni 200 mg/m²/day時則觀察到精子過少

當給予大鼠和兔子低於臨床曝露值的Sorafenib,會有胚胎毒性及致畸胎性。觀察到的影響包括母體及胎兒的體重減輕、增加 胎兒吸收次數,以及增加外部和內臟畸形的數目。 治療期間及療程完成後至少2週應採取適當的避孕措施

目前已針對肝細胞癌(HCC)、腎細胞癌(RCC)和分化型甲狀腺癌(DTC)病患進行Nexavar的臨床安全性和療效試驗。 14.1 肝細胞癌(Hepatocellular Carcinoma)

HCC試驗1(試驗100554)為針對無法手銜切除之肝細胞癌病患的一項全球、多中心、隨機、雙盲、安慰劑對照、第3期臨床試 。整體存活期為主要療效終點。共有602位病患接受隨機分配,299位被分配至每日雨次Nexavar 400 mg組,303位則被分配 至對應之安慰劑組

Nexavar組和安慰劑組有關年齡、性別、種族、表現狀態、病因學(包括B型肝炎、C型肝炎和酒精性肝臟疾病)、TNM疾病分期(第I期:<1%及<1%7、第II期:10.4%及8.3%;第III期:37.8%及43.6%;第IV期:50.8%及46.9%)、無肉眼可見的血管侵犯和 开外腫瘤擴散(30.1%及30.0%)和巴賽隆納肝癌治療準則分期(B期:18.1%及16.8%; C期:81.6%及83.2%; D期:< 1%及0%)的 人口統計資料和基線疾病特性均相似。Nexavar組和安慰劑組在以Child-Pugh評分的肝功能受損程度上亦相似(A級: 95%及 Nexavar組的無疾病惡化存活期中位數: 98%; B級: 5%及2%)。只有1位Child-Pugh C級病患參與試驗。曾接受之治療包括手術切除治療(19.1%及20.5%)。另有區域療 亡風險程度)為0.44 (95% CI: 0.35, 0.55)

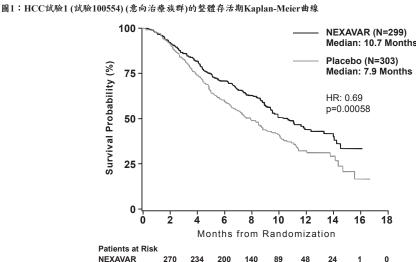
於預訂之第二次存活期中分析後即中止試驗,因證實在整體存活期方面,Nexavar组較安慰劑組具統計顯著效益(HR:0.69, = 0.00058) (參見表10和圖1)。次族群分析均有一致的優異表現。 使用於較早時間點(獨立的放射影像評估)取得的數據進行分析的結果顯示,Nexavar治療組的疾病無惡化時間(TTP)顯著較長

表9:基線病人特性;受試者為符合意向治療族群者		
	安慰劑	Nexavar
	(n=303)	(n=299)
Child-Pugh狀態n (%)		
A	297 (98%)	284 (95%)
В	6 (2%)	14 (5%)
C	0 (0%)	1 (0.3%)
實驗室檢測出肝炎n(%)		
僅C型肝炎	81 (27%)	86 (29%)
僅B型肝炎	28 (9%)	32 (11%)
B型及C型肝炎	3 (1%)	7 (2%)
C型肝炎抗體或B型肝炎表面抗原	165 (55%)	149 (50%)
血清學檢測陰性		
無資料	26 (9%)	25 (8%)

療效參數	Nexavar	安慰劑	風險比1	P值
	(N=299)	(N=303)	(95% CI)	(log rank test2)
整體存活期				
中位數,月數	10.7	7.9	0.69	0.00058
(95% CI)	(9.4, 13.3)	(6.8, 9.1)	(0.55, 0.87)	
事件數	143	178		
疾病無惡化時間3				
中位数,月数	5.5	2.8	0.58	0.000007
(95% CI)	(4.1, 6.9)	(2.7, 3.9)	(0.45, 0.74)	
事件数	107	156		

1. 風險比, Nexavar/安慰劑, Cox分層模型 2. Stratified log rank test (針對存活時間之期中分析,試驗停止條件為單尾alpha值= 0.0077)

以獨立放射影像評估進行之疾病無惡化時間(TTP)分析,使用在存活率分析之前取得的數據進行



大験100554中共納入602位病患,其中有168位病患(28%)從Child Pugh A級惡化至Child Pugh B級或C級,Nexavar組病患從Child Pugh A級惡化至基線後測得Child Pugh B級或C級的時間,較安慰劑組短(47天及84天),最重要的療效指標中位數整體存活 (257 天及171天)及疾病無惡化時間 (126天及80天), Nexavar組仍比安慰劑組長(參見表11)。由Albou-Alfa報告得知, Child-Pugh B之 病人使用Nexavar有較多的hyperbilirubinemia、encephalopathy及ascites。詳情請見references (G. K. Albou-Alfa et al. Is sorafenib safe and effective in patients with hepatocellular carcinoma (HCC) and Child-Pugh B (CPB) cirrhosis? Journal of Clinical Oncology. 2008 nual Meeting Proceedings (Post-Meeting Edition), Vol 26, No 155 (May 20 Supplement) 2008: 4518

	安慰劑	Nexavai
	(n=73)	(n=95)
基線特性		
Child-Pugh狀態(n)		
A	72	85
В	1	10
病因學(n)		
酒精	17	31
僅B型肝炎	12	14
僅C型肝炎	19	26
其他	11	8
不明	14	16
達Child Pugh B級之人數(n)	71	88
達Child Pugh C級之人數(n)	2	7
從基線至測得Child Pugh B級或C級的時間中位數	84天	47天
達Child Pugh B級或C級狀態後的治療時間中位數	22天	48天
此類受試者的整體存活(OS)中位數	171天	257天
疾病無惡化時間(TTP) (根據獨立評估結果)	80天	126天
6個月OS率	46%	62%
第3個月放射影像評估無疾病惡化率	38%	60%
第6個月放射影像評估無疼病惡化率	13%	41%

Sorafenib為激酶的抑制劑,在體外試驗中可降低腫瘤細胞增生。Sorafenib被證實可抑制多種細胞內(CRAF、BRAF和突變型 HCC試驗2(試驗11849)是一項納入226位肝細胞癌病患於中國、台灣和韓國進行的多中心、隨機、雙盲、安慰劑對照、第3期臨 BRAF)及細胞表面激酶(KIT, FLT-3、RET、VEGFR-1、VEGFR-2、VEGFR-3和PDGFR-β)反應。目前認為這些激酶中有數種與 床試驗。所有接受隨機分配的226位受試者皆為亞洲人。接受隨機分配的226位受試者中,分配至安慰劑组的有76位,至 療效分析結果顯示Nexavar在延長整體存活方面,顯著優於安慰劑(HR: 0.68, p=0.014)。疾病無惡化時間結果分析也顯示 Nexavar顯著優於安慰劑。安慰劑組之疾病無惡化時間中位數為41.5天,而Nexavar組為84天(HR:0.57,p<0.001)(參見表12)

整體存活期(OS 0.014 (114, 166)[中位數,日數(95% C] (0.50, 0.93)< 0.001 (41, 47)

CI=信賴區間, HR=風險比(Nexavar比安慰劑 14.2 腎細胞癌(Renal Cell Carcinoma)

下面二個隨機對照的臨床試驗研究Nexavar治療晚期腎細胞癌(RCC)的安全性及療效。

RCC試驗1(試驗11213)是一個針對曾接受一種全身性治療的晚期腎細胞癌病患所進行全球多中心、隨機、雙盲、安慰劑對照的 第三期臨床試驗。主要療效指標為總存活期(overall survival, OS)及無疾病惡化存活期(progression-free survival, PFS), 次要的療效 16.5 腸胃道穿孔 Sorafenib主要在肝臟中藉由CYP3A4氧化代謝,以及藉由UGT1A9醛糖酸作用(glucuronidation)進行代謝。Sorafenib共軛物會由 指標為腫瘤反應率(tumor response rate)。依MSKCC (Memorial Sloan Kettering Cancer Center)預後風險程度(low or intermediate)及國 家分組且隨機分配至每日雨次Nexavar 400mg组(N=384)或安慰劑组(N=385)的769名病患進行無疾病惡化存活期(PFS)的分析。 13為研究試驗群族人口統計資料及疾病特性之摘要。兩個治療組的基線人口統計資料及疾病特性相當平均,Nexavar組及安 慰劑組其從最初診斷為RCC到隨機分配所經歷時間的中位數分別為1.6年及1.9年。 表13:RCC試驗1(試驗11213)的人口統計資料及疾病特性

特性	Nexavar	組 N=384	安慰劑	組N=385	
	n	(%)	n	(%)	
性別					
男性	267	(70)	287	(75)	
女性	116	(30)	98	(25)	
種族					
白人	276	(72)	278	(73)	
黑人/亞洲人/西班牙人/其他	11	(3)	10	(2)	
未紀錄a	97	(25)	97	(25)	
年龄群					
小於65歲	255	(67)	280	(73)	
65歲以上(包括65歲)	127	(33)	103	(27)	
基線ECOG評估身體狀況等級					
0	184	(48)	180	(47)	
1	191	(50)	201	(52)	
2	6	(2)	1	(<1)	
未紀錄	3	(<1)	3	(< 1)	
MSKCC預後風險分級					
低	200	(52)	194	(50)	
中度	184	(48)	191	(50)	
曾IL-2及/或干擾素治療					
是	319	(83)	313	(81)	
否	65	(17)	72	(19)	

a 於法國納入的168名病患依當地法規並未紀錄其種族,另8名病患於分析時並未知道其種族。 PFS的定義是從隨機分配開始到任何原因的惡化或死亡(較早發生者),並藉由盲性且獨立放射性影像檢查並依腫瘤測量標準 RECIST)來評斷。圖2表示PFS的Kaplan-Meier曲線。PFS是依預後風險及國家分組的雙邊對數系列檢定(Log-Rank Test)來分析

—— NEXAVAR (N=384) Median: 167 Days Placebo (N=385) Median: 84 Day HR: 0.44 P<0.00000 60 120 180 240 300 360 Days From Randomization

註:HR是來自涵蓋下列共變數的Cox迴歸分析(Cox regression model):MSKCC預後風險分級及國家。P值是來自依預後風險及 國家分組的雙邊對數系列檢定來分析 Nexavar組的無疾病惡化存活期中位數是167天,比較安慰劑組是84天。估計危險比例(hazard ratio,Nexavar相對於安慰劑的死 Nexavar對無疾病惡化存活期的影響是一致的,包括之前未曾接受IL-2或干擾素治療的病患(n = 137; Nexavar組有65名而安慰劑

組有72名),而其無疾病惡化存活期中位數在Nexavar組為172天而安慰劑組為85天。 腫瘤反應是藉由獨立醫師檢查放射性影像並依腫瘤測量標準(RECIST)來評斷。整體而言可以分析反應的672名病患中,7名 Jexavar病患(0.2%)有經確認的局部反應;而無一安慰劑組病患有經確認的局部反應。因此Nexavar治療組病患PFS的延長主要 反應在穩定疾病族群。

於220個死亡案例時的期中存活率分析,相較於安慰劑組,Nexavar組在總存活期較長,危險比例(hazard ratio)估計為0.72。此 分析結果並未符合預先定義的顯著統計標準,計劃在存活資料齊全時再完成更多的分析。 RCC試驗2(試驗100391)是一個以轉移性惡性腫瘤病患(包括腎細胞癌)進行隨機停藥的第二期臨床試驗,主要療效指標為在24個 星期後病患仍無疾病惡化的比例。前12個星期所有病患皆以Nexavar治療。在第12週做放射性影像檢查,以二維法測量腫瘤大 小其變化小於25%之病患則再隨機分配至Nexavar組或安慰劑組進行再12個星期的試驗,隨機分配至安慰劑組的病患若有惡化 青形則允許改以Nexavar治療,腫瘤縮小25%以上的病患持續以Nexavar治療,腫瘤增大25%以上的病患則停止治療。202位晚 期腎細胞癌病患納入試驗2,其中包括先前未曾接受任何治療的病患,或非cancer cell carcinoma的病患。前12個星期的Nexavar 治療後,有79位RCC病患持續Nexavar治療而有65位被隨機分配至Nexavar组或安慰劑組。在另一個12個星期後,也就是第24 週,隨機分配的65病患中,隨機分配至Nexavar組的病患其無疾病惡化率(16/32,50%)明顯地大於安慰劑組(6/33,18%) (p=0.0077)。

Vexavar組的無疾病惡化存活期(163天)明顯地多於安慰劑組(41天)(p=0.0001, HR=0.29)

14.3 分化型甲狀腺癌 一項多中心、隨機分配(1:1)、雙盲及安慰劑對照的試驗,評估417位具局部復發或轉移、進行性且對放射性碘(RAI)治療具有 抗性的分化型甲狀腺癌(DTC)病患,建立了Nexavar的安全性及療效概況。隨機分配的分層依據為年齡(< 60歲及≥ 60歲)以及地 理區域(北美洲、歐洲及亞洲)。

所有病患均處於惡化活性期,其定義為疾病於納入14個月內出現惡化。RAI抗性定義有4個相互無衝突的標準。所有的RAI治 療及診斷性掃描,均在低碘飲食和適當的TSH刺激狀態下進行。下列為RAI抗性標準和試驗中符合該標準的受試者比例:RAI 掃描時,發現有一個目標病灶未購入碘(68%);在納入的16個月內,有攝入碘的腫瘤在RAI治療後惡化(12%);腫瘤可攝入碘 且經過複數次RAI治療,最後一次治療時間為納入前的16個月以上,且在相隔16個月之內的兩次RAI治療後疾病均惡化(7%) 所累積的RAI投予劑量≥600 mCi (34%)。治療成效的主要度量標準為無疾病惡化存活期(PFS),PFS的判定是根據調整後的實體 腫瘤反應評估標準第1.0版(RECIST),進行盲性且獨立的放射學審核。RECIST的調整之處為包括了骨骼病灶出現臨床性惡化,其判斷依據為需要進行體外放射治療(佔惡化事件的4.4%)。其他的治療成效度量標準包括總存活期(OS)、腫瘤反應率以 病患經隨機分配接受Nexavar 400毫克,每天雨次(n=207)或安慰劑(n=210)。417位隨機分配病患,有48%為男性、年齡中位數

,63歲、61%為60歲以上、60%為白人、62%病患其ECOG日常體能狀態為0分和及99%曾接受甲狀腺切除術。組織學診斷的 結果,乳突癌佔試驗族群57%、濾泡癌(包括Hürthle細胞)為25%、分化不良型的癌症為10%、其他則為8%。96%的病患出現轉 移現象:86%的病患轉移至肺、淋巴結為51%、骨骼為27%。進入試驗前,RAI活性的投予累積量中位數為400 mCi。 統計結果顯示Nexavar組,其PFS顯著大於安慰劑組。經試驗主持人認定為疾病惡化後,157位(75%)經隨機分配至安慰劑組安 慰劑治療的病患,改以開放性接受Nexavar治療,另外61 (30%)位經隨機分配至Nexavar組改以開放性Nexavar治療。這兩個治 療組的總存活期並無統計上的顯著差異(參見表14及圖3)。

Placebo組(N=210)

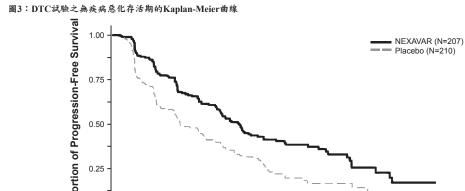
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表14:分化型甲狀腺癌試驗的療效結果

死亡或惡化的人數	113 (55%)	136 (65%)
PFS中位数(月) (95% CI)	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)
風險比(95% CI)	0.59 (0.4	46, 0.76)
P值 ²	<0.	001
總存活期3		
死亡人數	66 (32%)	72 (34%)
OS中位數(月) (95% CI)	NR	36.5 (32.2, NR)
風險比(95% CI)	0.88 (0.0	63, 1.24)
P值 ²	0.	47
目標反應		
具目標反應的人數4	24 (12%)	1 (0.5%)
(95%CI)	(7.6%, 16.8%)	(0.01%, 2.7%)
反應持續時間中位數(月)(95% CI)	10.2 (7.4, 16.6)	NE

2 雙邊對數等級檢定的分層依據為年齡(<60歲、≥60歲)以及地理區域(北美洲、歐洲、亞洲) 3於進行最終PFS分析而中止收集數據後的9個月進行

4 所有目標反應皆為部份反應 NR = 未達到, CI = 信賴區間, NE = 無法評估



Duration of Progression-Free Survival (mon Patients at Risk

蕾莎瓦錠劑是圓形、雙凸面、紅色口服膜衣錠,正面有Bayer十字標幟,反面有"200"。每錠含sorafenib tosylate,相當於200 錠劑芯: croscarmellose sodium、microcrystalline cellulose、hypromellose、sodium lauryl sulfate、 magnesium stearate

膜衣層: hypromellose、macrogol 3350、titanium dioxide、iron oxide red

0°C以下乾燥處儲存。藥品必須置於兒童無法觸及之處。

通報[參見警語和注意事項(6.1)]。 告知病患Nexavar會增加出血危險性且必須及時報告出血事件。 告知病患在Nexavar治療期間同時服用warfarin的患者中,曾有出血或國際標準凝血時間比(INR)升高的案例通報。這些病患應 該定期監測INR值[參見警語和注意事項(6.7)]。

醫師須與病患討論在Nexavar治療時曾有心缺血和/或心肌梗塞的案例,發生胸痛或心缺血和/或心肌梗塞的其他症狀時須立即

告知病患在Nexavar治療期間可能會發生高血壓,尤其在前六週治療期,治療期間都應定期監測血壓/參見警語和注意事項(6.4 16.4 皮膚反應

16.6 傷口癒合併發症

告知病患若接受大型外科手術,建議暫時中斷Nexavar [參見警語和注意事項(6.8)]。 16.7 OT間隔的延長 告知有QT間隔延長病史的患者,Nexavar會惡化狀況[參見警語和注意事項(6.2)]。

16.8 生產缺陷和失去胎兒 告知女性病患Nexavar會造成生產缺陷或失去胎兒。建議男性和女性患者在Nexavar治療期間及停止治療至少2個星期皆採用有效 的生育節制措施。告知女性患者若在服用Nexavar期間懷孕,要聯繫主治醫師[參見警語和注意事項(6.10) 特殊族群使用(9.1)]。

建議服用Nexavar期間不要餵哺母乳[參見特殊族群使用(9.3)] 指導患者若漏服一個劑量的Nexavar,於下個正常服藥的期間服用原本的劑量,不要將劑量加倍。指導患者若服用過多的

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Nexavar film-coated tablets 200mg / USPI_11/2013+CCDS21_12Jun2013 / TW11

PMR 86316617 Technical Template (O8/00-N) Pantone: Black, 2718, 186



.1 Hepatocellular Carcinoma

3 DOSAGE AND ADMINISTRA

NEXAVAR is indicated for the treatment of patients with metastatic or unresectable advanced hepatocellular carcinoma (HCC) and Statement: In the pivotal study for the HCC indication (study 100554), by Child-Pugh score the majority of enrolled groups are Child-Pugh and 25% had TSH levels greater than 4.4 mU/L. Class A and the minority are Child-Pugh class B patients [see Clinical Studies (14.1)].

Monitor TSH levels monthly and adjust thyroid rejection. 2.2 Renal Cell Carcinoma

nterleukin-2 based therapy or are considered unsuitable for such therapy. 2.3 Differentiated Thyroid Carcinoma

NEXAVAR is indicated for treatment of patients with locally advanced or metastatic ,progressive, differentiated thyroid carcinoma (DTC)

The recommended daily dose of NEXAVAR is 400 mg (2 x 200 mg tablets) taken twice daily without food (at least 1 hour before or 2 hours after a meal). For oral use. To be swallowed with a glass of water. Treatment should continue until the patient is no longer clinically enefiting from therapy or until unacceptable toxicity occurs <u>Dose modification for Hepatocellular Carcinoma and Renal Cell Carcinoma</u>

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of NEXAVAR therapy. When dose reduction is necessary, the NEXAVAR dose may be reduced to 400 mg once daily. If additional dose reduction is required, NEXAVAR may be reduced to a single 400 mg dose every other day [see Warnings and Precautions (6)]. Suggested dose modifications for skin toxicity are outlined in Table 1.

Table 1: Suggested Dose Modifications for Dermatologic Toxicities in Patients with hepatocellular or Renal Cell Carcinoma Dermatologic Toxicity Grade Occurrence Suggested Dose Modification Grade 1: Numbness, dysesthesia, paresthesia, tingling, Any occurrence Continue treatment with NEXAVAR and consider topical therapy for painless swelling, erythema or discomfort of the hands or symptomatic relief feet which does not disrupt the patient's normal activities Grade 2: Painful erythema and swelling of the hands or 1st occurrence | Continue treatment with NEXAVAR and consider topical therapy for feet and/or discomfort affecting the patient's normal symptomatic relief No improvement | Interrupt NEXAVAR treatment until toxicity resolves to Grade 0 within 7 days or | When resuming treatment, decrease NEXAVAR dose by one dose level | 2nd or 3rd (400 mg daily or 400 mg every other day) Grade 3: Moist desquamation, ulceration, blistering or 1st or 2nd Interrupt NEXAVAR treatment until toxicity resolves to Grade 0-

3rd occurrence Discontinue NEXAVAR treatment Dose modifications for Differentiated Thyroid Carcinoima Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of NEXAVAR therapy.

causes the patient to be unable to work orperform

activities of daily living

When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the NEXAVAR dose should be reduced to 600mg daily in divided doses (two tablets of 200 mg and one tablet of 200 mg welve hours apart). If additional dose reduction is necessary, NEXAVAR may be reduced to one tablet of 200 mg twice daily, followed by one tablet of 200 mg once daily. After improvement of on-hematological adverse reactions, the dose of NEXAVAR may be increased Table 2: Recommended Doses for Patients with Differentiated Thyroid Carcinoma Requiring Dose Reduction

severe pain of the hands or feet, or severe discomfort that occurrence When resuming treatment, decrease NEXAVAR dose by one dose level

(400 mg daily or 400 mg every other day)

600 mg daily dose 400 mg and 200 mg 12 hours apart (2 tablets and 1 tablet 12 hours apart – either dose can come first) Second Dose Reduction 400 mg daily dose 200 mg twice daily (1 tablet twice daily)

Third Dose Reduction 200 mg daily dose 200 mg once daily (1 tablet once daily When dose reduction is necessary for dermatology toxicities, reduce the NEXAVAR dose as indicated in Tablet 3 below

Dermatologic Toxicity Grade	Occurrence	NEXAVAR Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling,	Any occurrence	Continue treatment with NEXAVAR
painless swelling, erythema or discomfort of the hands or		
feet which does not disrupt the patient's normal activities		
Grade 2: Painful erythema and swelling of the hands or	1st occurrence	Decrease NEXAVAR dose to 600 mg daily
feet and/or discomfort affecting the patient's normal		If no improvement within 7 days, see below
activities	No improvement within 7 days	Interrupt NEXAVAR until resolved or improved to grade 1
	at reduced dose or 2nd	If NEXAVAR is resumed, decrease dose (see Table 2)
	Occurrence	
	3 rd occurrence	Interrupt NEXAVAR until resolved or improved to grade 1
		If NEXAVAR is resumed, decrease dose (see Table 2)
	4 th occurrence	Discontinue NEXAVAR permanently
Grade 3: Moist desquamation, ulceration, blistering, or	1 st occurrence	Interrupt NEXAVAR until resolved or improved to grade 1
severe pain of the hands or feet, resulting in inability to		If NEXAVAR is resumed, decrease dose by one dose lev
work or perform activities of daily living		(see Table 2)
	2 nd occurrence	Interrupt NEXAVAR until resolved or improved to grade 1
		When NEXAVAR is resumed, decrease dose by two dose
		levels (see Table 2)
	3 rd occurrence	Discontinue NEXAVAR permanently

NEXAVAR, the dose of NEXAVAR may be increased one dose level from the reduced dose. Approximately 50% of patic reduction for dermatologic toxicity are expected to meet these criteria for resumption of the higher dose and roughly 50% of patients resuming the previous dose are expected to tolerate the higher dose (that is, maintain the higher dose level without recurrent Grade 2 or

No dose adjustment is required on the basis of patient age, gender, or body weight.

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers may decrease sorafenib plasma concentrations and should be avoided (eg, St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). Although a dose increase has not been studied, if a strong CYP3A4 inducer must be co-administered, a NEXAVAR dose increase may be of the dose of NEXAVAR is increased, the patient should be monitored carefully for toxicity [see DRUG INTERACTIONS (8.7)]. Tablets containing sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib.

NEXAVAR tablets are round, biconvex, red film-coated tablets for oral use with a diameter of 10 mm and a weight of 350 mg, debossed with the "Bayer cross" on one side and "200" on the other side.

• NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVA • NEXARVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer [see 6 warning

NEXAVAR-treated patients in the DTC study.

6.1 Risk of Cardiac Ischemia and/or Infarction In the HCC study, the incidence of cardiac ischemia/infarction was 2.7% in NEXAVAR patients compared with 1.3% in the placebo-treate group, in RCC Study 1, the incidence of cardiac ischemia/infarction was higher in the NEXAVAR-treated group (2.9%) compared with the ated group (0.4%), and in the DTC study, the incidence of cardiac ischemia/infarction was 1.9% in the NEXAV compared with 0% in the placebo-treated group. Patients with unstable coronary artery disease or recent myocardial infarction were cluded from this study. Temporary or permanent discontinuation of NEXAVAR should be considered in patients who develop cardiac ischemia and/or infarction

6.2 QT interval prolongation NEXAVAR has been shown to prolong the QT/QTc interval (see Pharmacological Properties - Pharmacodynamics), which may lead to an ncreased risk for ventricular arrhythmias. Use sorafenib with caution in patients who have, or may develop prolongation of QTc, such as patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia. When using NEXAVAR in these patients, periodic monitoring with on-treatment ocardiograms and electrolytes (magnesium, potassium, calcium) should be considered

6.3 Risk of Hemorrhage An increased risk of bleeding may occur following NEXAVAR administration. In the HCC study, an excess of bleeding regardless of Laboratory abnormalities in HCC patients (study 100554) causality was not apparent and the rate of bleeding from esophageal varices was 2.4% in NEXAVAR-treated patients and 4% in placeboding with a fatal outcome from any site was reported in 2.4% of NEXAVAR-treated patients and 4% in placebo-ti patients. In RCC Study 1, bleeding regardless of causality was reported in 15.3% of patients in the NEXAVAR-treated group and 8.2% of roup. The incidence of CTCAE Grade 3 and 4 bleeding was 2% and 0%, respectively, in NEXAVAR-treated patients, and 1.3% and 0.2%, respectively, in placebo-treated patients, and 1.3% and 0.2%, respectively, in placebo-treated patients. There was one fatal hemorrhage in each treatment group in RCC Study 1. In the DTC study, bleeding was reported in 17.4% of NEXAVAR-treated patients and 9.6% of placebo-treated patients, however the incidence of CTCAE Grade 3 bleeding was 1% in NEXAVAR-treated patients and 1.4% in placebo-treated patients. There was no Grade

Ear and Labyrinth Disorders

Group; there was 1 case of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in the placebo group. The etiology of hypophosphatemia associated with NEXAVAR is not known.

Elevated lipase was observed in 40% of patients treated with NEXAVAR compared to 37% of patients in the placebo group. CTCAE Grade 2 hypophosphatemia (<1 mg/dL) reported in the placebo group. The etiology of hypophosphatemia associated with NEXAVAR is not known.

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6.4 Risk of Hypertension Monitor blood pressure weekly during the first 6 weeks of NEXAVAR. Thereafter, monitor blood pressure and treat hypertension, if required, in accordance with standard medical practice. In the HCC study, hypertension was reported in approximately 9.4% of NEXAVAR-treated reated patients and 1.8% of patients in the placebo-treated group. In the DTC study, hypertension was reported in 40.6% of NEXAVAR-treated patients and 2% of placebo patients; there was no CTCAE Grade 4 INR elevation in either group treated patients and 12.4% of placebo-treated patients. Hypertension was usually mild to moderate, occurred early in the course of Lymphopenia was observed in 47% of NEXAVAR-treated patients and 42% of placebo patients. ment, and was managed with standard antihypertensive therapy. In cases of severe or persistent hypertension of hypertensive therapy, consider temporary or permanent discontinuation of NEXAVAR. Permanent discontinuation due to hypertension was observed in 46% of NEXAVAR-treated patients and 41% of placebo patients; CTCAE Grade 3 or 4 thrombocytopenia was observed in 46% of NEXAVAR-treated patients and 41% of placebo-treated patients.

Thrombocytopenia was observed in 46% of NEXAVAR-treated patients and 41% of placebo-treated patients.

and Mediastinal Disorders

Disorders antihypertensive therapy, consider temporary or permanent discontinuation of NEXAVAR. Permanent discontinuation due to hypertension urred in 1 of 297 NEXAVAR-treated patients in the HCC study, and 1 of 451 NEXAVAR-treated patients in RCC Study 1, and 1 of 207

6.5 Risk of Dermatologic Toxicities Hand-foot skin reaction and rash represent the most common adverse reactions attributed to NEXAVAR. Rash and hand-foot skin reaction are usually CTC (National Cancer Institute Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of compared to 6% of patients receiving placebo. treatment with NEXAVAR. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of NEXAVAR, or in severe or persistent cases, permanent discontinuation of NEXAVAR. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 4 of 297 NEXAVAR-treated patients with HCC and 3 of 451 NEXAVAR-treated patients with RCC, and 11 (5.3%) of 207 NEXAVAR-treated patients with DTC.

There have been reports of severe dermatologic toxicities, including Stevens-Johnson syndrome (SJS) and toxicepidermal necrolysis (TEN). These cases may be life-threatening. Discontinue NEXAVAR if SJS or TEN are suspected. 6.6 Risk of Gastrointestinal Perforation

Gastrointestinal perforation is an uncommon adverse reaction and has been reported in less than 1% of patients taking NEXAVAR. In some cases this was not associated with apparent intra-abdominal tumor. In the event of a gastrointestinal perforation, discontinue NEXAVAR. nfrequent bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR therapy. Monitor patients taking concomitant warfarin regularly for changes in prothrombin time (PT), INR or clinical bleeding

6.8 Wound Healing Complications No formal studies of the effect of NEXAVAR on wound healing have been conducted. Temporary interruption of NEXAVAR therapy is ecommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of NEXAVAR therapy following major surgical intervention Therefore, the decision to resume NEXAVAR therapy following a major surgical intervention should be based on clinical judgment of

6.9 Interaction with Neomycin Co-administration of neomycin may cause a decrease in sorafenib bioavailability [see Drug-Drug Interactions (8.5)]. 6.10 Risk of Fetal harm

There are no adequate and well-controlled studies in pregnant women using NEXAVAR. However, based on its mechanism of action and findings in animals, NEXAVAR may cause fetal harm when administered to a pregnant woman. Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. Advise women of childbearing potential to avoid becoming pregnant while on NEXAVAR because of the potential hazard to the fetus [see Use in Specific Populations (9.1)]. Hepatic impairment may reduce plasma concentrations of sorafenib. Comparison of data across studies

suggests that sorafenib levels are lower in HCC patients than in non-HCC patients (without hepatic impairment). The AUC of sorafenib is similar between HCC patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. The optimal dose in non-HCC patients with hepatic impairment is not established [see Use in Specific Populations (9.7) and Clinical Pharmacology (12.2)]

6.12 Increased Mortality Observed with NEXAVAR Administered in Combination with Carboplatin/Paclitaxel and Gemcitabine/
The rate of adverse reactions (including those associated with progressive disease) resulting in permanent discontinuation was similar in In a subset analysis of two randomized controlled trials in chemo-naive patients with Stage IIIB-IV non-small cell lung cancer, patients with Laboratory Abnormalities squamous cell carcinoma experienced higher mortality with the addition of NEXAVAR compared to those treated with carboplatin/paclitaxel

The following laboratory abnormalities were observed in RCC patients in Study 1 (Study 11213):

alone (HR 1.81, 95% Cl 1.19–2.74) and gemcitabine/cisplatin alone (HR 1.22, 95% Cl 0.82-1.80). The use of NEXAVAR in combination with Hypophosphatemia was a common laboratory finding, observed in 45% of NEXAVAR-treated patients compared to 11% of placebo-treated 7.5 Additional information on special populations carboplatin/paclitaxel is contraindicated in patients with squamous cell lung cancer. NEXAVAR in combination with gemeitabline/cisplatin is not recommended in patients with squamous cell lung cancer. NEXAVAR has not been established in group. There were no cases of CTCAE Grade 4 hypophosphatemia (1–2 mg/dL) reported in either NEXAVAR or placebo-treated patients. The etiology of hypophosphatemia associated with NEXAVAR is not known. patients with non-small cell lung cancer [see Undesirable effects (7.5)] 6.13 Hypocalcaemia

When using NEXAVAR in patients with differentiated thyroid carcinoma, close monitoring of blood calcium level is recommended. In clinical trials, hypocalcaemia was more frequent and more severe in patients with differentiated thyroid carcinoma, especially with a history of parathyroidism, compared to patients with renal cell or hepatocellular carcinoma [see Undesirable effects (7.3), 6.14 Impairment of Thyroid Stimulating Hormone Suppression in Differentiated Thyroid Carcinoma

NEXAVAR impairs exogenous thyroid suppression. In the DTC study, 99% of patients had a baseline thyroid stimulating hormone (TSH) level less than 0.5 mU/L. Elevation of TSH level above 0.5 mU/L was observed in 41% of NEXAVAR-treated patients as compared with 16% cebo-treated patients. For patients with impaired TSH suppression while receiving NEXAVAR, the median maximal TSH was 1.6 mU/L Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC.

Clinically it should be examined carefully and receive assessment and appropriate management by dermatologists in case of detecting 7.3 Adverse Reactions in DTC Study

6.15 Keratoacanthoma and skin squamous cell carcinoma NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have failed prior interferon-alpha or When using NEXAVAR, keratoacanthoma and skin squamous cell carcinoma may be occurred. In DTC study, 8 cases of skin squamous cell carcinoma have been reported in NEXAVAR group (7 cases from the double blind period and 1 case from the open label period), compared to control group is zero. Among these 8 patients with skin squamous cell carcinoma, all were recovered after surgical treatment.

The following serious adverse reactions are discussed elsewhere in the labeling:

• Cardiac ischemia, infarction [See Warnings and Precautions (6.1)] Hemorrhage [See Warnings and Precautions (6.3)]

Hypertension [See Warnings and Precautions (6.4)] Hand-foot skin reaction, rash, Stevens-Johnson syndrome, and toxic epidermal necrolysis [See Warnings and Precautions (6.5)] Gastrointestinal perforation [See Warnings and Precautions (6.6)]

• QT Interval Prolongation [see Warnings and Precautions (6.2) and Pharmacodynamics (12.3)] •Impairment of TSH suppression in DTC [see Warnings and Precautions (6.14)]

In addition, the following medically significant adverse reactions were uncommon during clinical trials of NEXAVAR: transient ischemic attack, arrhythmia, and thromboembolism. For these adverse reactions, the causal relationship to NEXAVAR has not been established 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 described in sections 7.1, 7.2 and 7.3 reflect exposure to NEXAVAR in 955 patients who participated in placebo controlled studies n hepatocellular carcinoma (n=297) or advanced renal cell carcinoma (n=451), or differentiated thyroid carcinoma (N = 207) The most common adverse reactions (≥20%), which were considered to be related to NEXAVAR, in patients with HCC, RCC or DTC are fatigue, infection, weight loss, decreased appetite, rash, hand-foot skin reaction, alopecia, diarrhea, nausea, gastrointestinal and abdominal pain, hypertension, and hemorrhage 7.1 Adverse Reactions in HCC Study

Table 4 and 5 shows the percentage of patients with HCC experiencing adverse reactions that were reported in at least 10% of patients and at a higher rate in the NEXAVAR arm than the placebo arm. CTCAE Grade 3 adverse reactions were reported in 39% of patients receiving NEXAVAR compared to 24% of patients receiving placebo. CTCAE Grade 4 adverse reactions were reported in 6% of patients receiving NEXAVAR compared to 24% of patients receiving placebo. NEXAVAR compared to 8% of patients receiving placebo.

		NEXAVAR N=297			Placebo N=302	
Adverse Event*	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
NCI- CTCAE v3 Category/Term	%	%	%	%	%	%
Any Event	98	39	6	96	24	8
Constitutional symptoms						
Fatigue	46	9	1	45	12	2
Weight loss	30	2	0	10	1	0
Dermatology/ Skin						
Rash/ desquamation	19	1	0	14	0	0
Pruritus	14	<1	0	11	<1	0
Hand-foot skin reaction	21	8	0	3	<1	0
Dry skin	10	0	0	6	0	0
Alopecia	14	0	0	2	0	0
Gastrointestinal						
Diarrhea	55	10	<1	25	2	0
Anorexia	29	3	0	18	3	<1
Nausea	24	1	0	20	3	0
Vomiting	15	2	0	11	2	0
Constipation	14	0	0	10	0	0
Hepatobiliary/ pancreas						
Liver dysfunction	11	2	1	8	2	1
Pain [']						
Pain, abdomen	31	9	0	26	5	1

CTCAE grade 3 hypertension was reported in 4% of NEXAVAR-treated patients and 1% of placebo treated patients. No patients were reported with CTCAE grade 4 reactions in either treatment group. Hemorrhage/bleeding was reported in 18% of those receiving NEXAVAR and 20% of placebo-treated patients. The rates of CTCAE grade 3 and 4 bleeding were also higher in the placebo group (CTCAE grade 3 - 3% NEXAVAR and 5% placebo and CTCAE grade 4 - 2% NEXAVAR and 4% placebo). Bleeding from esophageal varices was reported in 2.4% in NEXAVAR- treated patients and 4% of placebotreated patients.

Renal failure was reported in < 1% of patients treated with NEXAVAR and 3% of placebo treated patients. The rate of adverse reactions (including those associated with progressive disease) resulting in permanent discontinuation was similar in

NCI-CTCAE v3		EXAVAR (N = 149			Placebo (N = 75)	
System organ class /	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Preferred term	%	%	%	%	%	%
Any Adverse Reaction	98	36	9	95	31	7
Blood/Bone Narrow						
Hemoglobin	20	4	4	15	0	0
Leukocytes	11	1	0	8	4	0
Platelets	22	4	2	13	1	0
Cardiac General						
Hypertension	22	3	0	5	1	0
Constitutional Symptoms						
Fatigue	34	5	0	20	4	0
Fever	26	2	0	11	3	0
Weight Loss	42	3	0	17	1	0
Dermatology/Skin						
Alopecia	27	0	0	1	0	0
Hand-foot skin reaction	46	11	0	3	0	0
Pruritus	12	0	0	12	1	0
Rash/Desquamation	22	1	0	9	0	0
Gastrointestinal						
Anorexia	31	3	0	17	3	0
Ascites	26	7	0	17	9	0
Diarrhea	42	7	0	16	0	0
Metabolic/Laboratory	-					
Alkaline phosphatase	26	4	0	19	1	0
ALT	32	5	1	24	7	0
AST	41	18	1	31	15	4
Bilirubin	36	12	5	32	7	11
Hypoalbuminemia	22	0	Ô	21	0	0
Hyponatremia	15	8	1	13	8	0
Hypophosphatemia	11	3	'n	5	1	Õ
Lipase	13	2	0	5	Ó	0
Pain		-	Ŭ		•	· ·
Pain, abdomen nos	35	7	0	20	4	0
Pain, back	15	3	0	12	1	0
i uiii, buok	1 '0	J	U	1 '-		J

Ilmonary/Upper respiratory

The following laboratory abnormalities were observed in patients with HCC: Hypophosphatemia was a common laboratory finding, observed in 35% of NEXAVAR-treated patients compared to 11% of placebo patients; CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 11% of NEXAVAR- treated patients and 2% of patients in the placebo

4 bleeding reported and there was one fatal hemorrhage in a placebo-treated patient. If any bleeding necessitates medical intervention, permanent discontinuation of NEXAVAR should be considered. Due to the potential risk of bleeding, tracheal, bronchial, and esophageal infiltration should be treated with local therapy prior to administering NEXAVAR in patients with DTC.

3 or 4 lipase elevations occurred in 9% of patients in each group. Elevated amylase was observed in 34% of patients in each group. CTCAE Grade 3 or 4 amylase elevations were reported in 2% of patients in each group. CTCAE Grade 3 or 4 amylase elevations were transient, and in the majority of cases, NEXAVAR treatment was not interrupted. Clinical ancreatitis was reported in 1 of 297 NEXAVAR-treated patients (CTCAE Grade 2). Elevations in liver function tests were comparable between the 2 arms of the study. Hypoalbuminemia was observed in 59% of NEXAVAR-treated patients and 47% of placebo patients; no CTCAE Grade 3 or 4 hypoalbuminemia was observed in either group. patients and 4.3% of patients in the placebo group. In RCC Study 1, hypertension was reported in approximately 16.9% of NEXAVARINR elevations were observed in 42% of NEXAVAR-treated patients and 34% of placebo patients; CTCAE Grade 3 INR elevations were

7.2 Adverse Reactions in RCC Study 1 (Study 11213) Table 6 shows the percentage of RCC patients experiencing adverse events that were reported in at least 10% of patients and at a higher ate in the NEXAVAR Arm than the placebo arm. CTCAE Grade 3 adverse events were reported in 31% of patients receiving NEXAVAR

compared to 22% of patients receiving placebo. CTCAE Grade 4 adverse events were reported in 7% of patients receiving NEXAVAR

Adverse Reactions		NEXAVAR N=451			Placebo N=451	
NCI-CTCAE v3	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Category/Term	%	%	%	%	%	%
ny Adverse Reactions	95	31	7	86	22	6
ardiovascular, General						
Hypertension	17	3	<1	2	<1	0
onstitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
ermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand -foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
astrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
emorrhage/bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1
eurology						
Neuropathy-sensory	13	<1	0	6	<1	0
ain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	6	<1	Ö
Pain, headache	10	<1	0	6	<1	Ö
ulmonary						
Dyennea	1/	2	~1	12	2	-1

both the NEXAVAR and placebo groups (10% of NEXAVAR patients and 8% of placebo patients)

prombocytopenia was reported in 1% of NEXAVAR-treated patients and in no placebo-treated patients.

[Between Arm Difference of ≥ 5% (All Grades)¹ or ≥ 2% (Grades 3 and 4)]

Class & Preferred Term

odominal pai

General disorders an

Decreased appetite

Metabolism and nutrition disorders

guamous cell carcinoma of sk

Nervous system disorders

Laboratory Abnormalities

System Disorders

Metabolism and

Disorders

Skin and

Connective Tissue

Genitourinary

and Bone Disorders

Disorders Reproductive System

and Breast Disorders

General Disorders

Site Conditions

Subcutaneous Tissue | rash

Nutrition Disorders

Isee Adverse Reactions (7.1, 7.2)

haemorrhage, and hypertension/hypertensive crisis.

palmar-plantar erythrodysaesthesia syndrome in MedDRA

l gastrointestinal*

hypertension

nausea

hand-foot skir

and Administration pain (including mouth, influenza like illness

abdominal, bone,

tumour pain and

increased amylase

weight decreased

palmar-plantar erythrodysaethesia syndrome in MedDRA

pruritus

cerebral hemorrhage

Musculoskeletal and connective tissue disorder

Neoplasms benign, malignant and unspecified

Respiratory, thoracic and mediastinal disorders

National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0

7.4 Additional Data from Multiple Clinical Trials or Though Post-Marketing Use

rare ($\geq 1/10.000$ to < 1/1.000), not known (cannot be estimated from the data available).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

neutropenia

l hypokalemia

neuropathy

dysguesia

congestive hear

nyocardial ischemia

and/or infarction*

I dvsphonia

dry mouth and

reflux disease

dermatitis exfoliative

skin desquamation

hyperkeratosis

muscle spasms

mucosal inflammation

transaminases

renal failure

glossodynia)

dysphagia

hyponatraemia

3. Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation

6. Includes the following terms: hypertension, blood pressure increased, blood pressure systolic increased

Includes the following terms: oral pain, oropharyngeal discomfort, glossitis, burning mouth syndrome, glossodynia
 Palmar-plantar erythrodysesthesia syndrome (Hand-foot skin reaction)

Skin and subcutaneous tissue disorder

NEXAVAR N = 207

ncludes the following terms: abdominal pain, abdominal discomfort, hepatic pain, esophageal pain, esophageal discomfort, abdominal pain low abdominal pain upper, abdominal tenderness, abdominal rigidity

Elevated TSH levels are discussed elsewhere in the labeling [see Warnings and Precautions (6.14)]. The relative increase for the following laboratory abnormalities observed in NEXAVAR-treated DTC patients as compared to placebo-treated patients is similar to that observed in the RCC and HCC studies: lipase, amylase, hypokalemia, hypophosphatemia, neutropenia, lymphopenia, anemia, and thrombocytopenia

Serum ALT and AST elevations were observed in 59% and 54% of the NEXAVAR-treated patients as compared to 24% and 15% of

The most important serious adverse reactions were myocardial infarction/ischaemia, gastrointestinal perforation, drug induced hepatits

The most common adverse reactions were diarrhoea, fatigue, rash, alopecia, infection and hand-foot skin reaction (corresponds to

Adverse reactions reported in multiple clinical trials or through postmarketing use are listed below in Table 8, by system organ class (in MeDRA) and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 to < 1/100), uncommon (≥1/1,000 to < 1/100)

hypersensitivity reactions

and urticaria)

reversible posterio

interstitial lung

disease-like events

pneumonitis, acute

interstitial pneumona

monitis and lung

ease in bilirubin and drug induced

dermatitis

Nephrotic syndrome

Stevens-Johnson

iaundice, cholecystitis. | hepatitis

ammatiion etc

gastritis

mous cell cancer of the erythema multiforme

erectile dysfunction gynaecomastia

hese adverse reactions may have a life-threatening or fatal outcome. Such events are either uncommon or less frequent than uncommo

blood alkaline

phosphatase

prothrombin leve

gastrointestinal

neumonitis, radiatio

leukoencephalopathy

cluding skin reactions

with 11% of placebo-treated patients (3% ≥ Grade 3). In the DTC study, serum calcium levels were monitored monthly.

Table 8 : All Adverse Drug Reactions reported in patients in multiple clinical trials or through post-marketing use

 System Organ Class
 Very Common ≥ 1/10
 Common ≥ 1/100 to < 1/10</th>
 Uncommon ≥ 1/10,000 to < 1/100</th>
 Rare ≥ 1/10,000 to < 1/100</th>

 Infections and Infection
 infection
 folliculitis

Grades 3 and 4 All Grades

Two randomized placebo-controlled trials comparing safety and efficacy of sorafenib in combination with doublet platinum-based chemotherapies (carboplatin/paclitaxel and separately gemicitabine/cisplatin) versus the respective doublet platinum-based chemotherapies alone as first-line treatment for patients with advanced Non-Small Cell Lung Carcinoma (NSCLC) did not meet their primary endpoint of improved overall survival. Safety events were generally consistent with those previously reported. However, in both trials, higher mortality was observed in the subset of patients with squamous cell expenditure of the lung daylet at lateral versus to the dose excreted in feeces, and 19% of the dose excreted in reces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found expenditure to the control of the lung to the dose excreted in feeces, and 19% of the dose excreted in feeces, and 19% of the dose excreted in feeces, and 19% of the dose excreted in recession of the lung to the dose excreted in feeces, and 19% of the dose excreted in feeces. Elevated lipase was observed in 41% of patients treated with NEXAVAR compared to 30% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the NEXAVAR-treated group compared to 7% of patients in the placebo –treated group. Elevated amylase was observed in 30% of patients treated with NEXAVAR compared to 23% of patients in the placebo-treated arcinoma of the lung treated with sorafenib and doublet platinum-based chemo alone (paclitaxel/carboplatin: HR 1.81, 95% Cl 1.19-2.74; gemcitabine/cisplatin: HR 1.22, 95% Cl 0.82 – 1.80). No definitive cause was identified for the proup. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the NEXAVAR-treated group compared to 3% of patients in the placebo-treated group. Many of the lipase and amylase elevations were transient, and in the majority of cases NEXAVAR treatment in clinical

In clinical trials, certain adverse drug reactions such as hand - foot skin reaction, diarrhea, alopecia, weight decrease, hypertension, hypocalcaemia, and was not interrupted. Clinical pancreatitis was reported in 3 of 451 NEXAVAR-treated patients (one CTCAE Grade 2 and two Grade 4) and 1 of 451 patients (CTCAE Grade 2) in the placebo group.

Lymphopenia was observed in 23% of NEXAVAR-treated patients and 13% of placebo patients. CTCAE Grade 3 or 4 lymphopenia was reported in 13% of NEXAVAR-treated patients and 7% of placebo patients. Neutropenia was observed in 18% of NEXAVAR-treated patients and 10% of placebo patients. CTCAE Grade 3 or 4 neutropenia was reported in 5% of NEXAVAR-treated patients and 2% of placebo Caution is recommended when administering NEXAVAR with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan). In vitro data show that sorafenib inhibits glucuronidation by the UGT1A1 (Ki value: 1 µM) and UGT1A9 (Ki value: 2 µM) pathways. Concomitant clinical administration of NEXAVAR with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, resulted in a 67-120% increase in the AUC of SN-38. Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with NEXAVAR. Anemia was observed in 44% of NEXAVAR-treated patients and 49% of placebo-treated patients. CTCAE Grade 3 or 4 anemia was reported in 2% of NEXAVAR-treated patients and 4% of placebo-treated patients. rombocytopenia was observed in 12% of NEXAVAR-treated patients and 5% of placebo-treated patients. CTCAE Grade 3 or 4

8.2 Docetaxel

oncomitant use of docetaxel (75 or 100 mg/m² administered every 21 days) with NEXAVAR (200 or 400 mg twice daily administered on Day 2 through 19 The safety of NEXAVAR was evaluated in 416 patients with locally recurrent or metastatic, progressive differentiated thyroid carcinoma DTC) refractory to radioactive iodine (RAI) treatment randomized to receive 400 mg twice daily NEXAVAR (n=207) or matching placebo =209) until disease progression or intolerable toxicity in a double-blind trial (see Clinical Studies (14.3)). The data described below reflec

concomitant treatment with NEXAVAR resulted in a 21% increase in the AUC of doxorubicin. Although the clinical significance of these findings is unknown, median exposure to NEXAVAR for 46 weeks (range 0.3 to 135). The population exposed to NEXAVAR was 50% male, and had a median caution is recommended when administering doxorubicin with NEXAVAR. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67 120% increase in the QT interval prolongatio ose interruptions for adverse reactions were required in 66% of patients receiving NEXAVAR and 64% of patients had their dose reduced Drug-related adverse reactions that resulted in treatment discontinuation were reported in 14% of NEXAVAR-treated patients compared to 1.4% of placebo-treated patients. precautions for use).

Table 7 shows the percentage of DTC patients experiencing adverse reactions at a higher rate in NEXAVAR-treated patients than placebo-treated patients in the double-blind phase of the DTC study. CTCAE Grade 3 adverse reactions occurred in 53% of NEXAVAR. Caution is eated patients compared to 23% of placebo-treated patients. CTCAE Grade 4 adverse reactions occurred in 12% of NEXAVAR-treated recommended when NEXAVAR is co-administered with fluorouracil/le

Table 7 : Per-Patient Incidence of Selected Adverse Reactions Occurring at a Higher Incidence in NEXAVAR-Treated Patients Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate GI flora, interferes with the enterohepatic recycling of sorafenib (see Carcinogenicity studies have not been performed with sorafenib above), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average bioav decreased by 54%. The clinical significance of these findings for is unknown. Effects of other antibiotics have not been studied, but will likely depend on their

> 8.6 CYP2B6 and CYP2C8 Substrates Sorafenib inhibits CYP2B6 and CYP2C8 in vitro with Ki values of 6 and 1-2 µM, respectively. In a separate clinical study, concomitant administration of sorafenib with paclitaxel resulted in an increase, instead of a decrease, in the exposure of 6-OH paclitaxel, the active metabolite of paclitaxel that is formed v CYP2C8. These data sugget that sorafenib may not be an in vivo inhibitor of CYP2C8. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with NEXAVAR. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with NEXAVAR.

8.7 CYP3A4 Inducers Continuous concomitant administration of NEXAVAR and rifampicin resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity (e.g. Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations. [see Dosage and Administration (3)].

In vitro data indicate that sorafenib is metabolized by CYP3A4 and UGT1A9 pathways. Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days did not alter the mean AUC of a single oral 50 mg dose of sorafenib in healthy volunteers. Therefore, clinical pharmacokinetic teractions of sorafénib with CYP3A4 inhibitors are unlike Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4 as indicated by Ki values

ncomitant clinical administration of midazolam, dextromethorphan, and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6, and CYP2C19, respectively, following 4 weeks of sorafenib administration did not alter the exposure cyclophosphamide f these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. dministration of NEXAVAR 400 mg twice daily for 28 days did not alter the exposure of concomitantly administered midazolam (CYP3A4 substrate)

8.10 Combination with Other Antineoplastic Agents

In clinical studies, sorafenib has been administered together with a variety of other anti-neoplastic agents at their commonly used dosing regimens, including gemcitabine, cisplatin, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, docetaxel, irinotecan, and cyclophosphamide. Sorafenib had no clinically relevant effect on the pharmacokinetics of gemcitabine, cisplatin, carboplatin, oxaliplatin, or cyclophosphamide. 8.11 Paclitaxel/Carboplatin

Administration of paclitaxel (225 mg/m²) and carboplatin (AUC = 6) with sorafenib (≤ 400 mg twice daily), administered with a 3-day break in sorafenib dosing ound administration of paclitaxel/carboplatin, resulted in no significant effect on the pharmacokinetics of paclitaxel. See Drug Interactions (7.1, 7.2, 7.3 and 7.4) for information about interactions with irinotecan, docetaxel, doxorubicin and fluorouracil/ leucovorin. Co-administration of paclitaxel (225 mg/m², once every 3 weeks) and carboplatin (AUC=6) with sorafenib (400 mg twice daily, without a break in sorafenib ising) resulted in a 47% increase in sorafenib exposure, a 29% increase in paclitaxel exposure and a 50% increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin were unaffected. hese data indicate no need for dose adjustments when paclitaxel and carboplatin are co-administered with sorafenib with a 3-day break in sorafenib dosing. The clinical significance of the increases in sorafenib and paclitaxel exposure, upon co-administration of sorafenib without a break in dosing, is unknowr

8.12 Capecitabine Co-administration of capecitabine (750-1050 mg/m² twice daily. Days 1-14 every 21 days) and sorafenib (200 or 400 mg twice daily, continuous uninterrupted ministration) resulted in no significant change in sorafenib exposure, but a 15-50% increase in capecitabine exposure and a 0-52% increase in 5-F osure. The clinical significance of these small to modest increases in capecitabine and 5-FU exposure when co-administered with sorafenib is unkno USE IN SPECIFIC POPULA

Pregnancy Category D Isee Warnings and Precautions (6.10). Based on its mechanism of action and findings in animals, NEXAVAR may cause fetal harm when administered to a pregnant woman. Sorafenib caused

embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. There are no adequate and well-controlled studies in pregnant women using NEXAVAR. Inform patients of childbearing potential that NEXAVAR can placebo-treated patients, respectively. High grade (≥ 3) ALT and AST elevations were observed in 4% and 2%, respectively, in the NEXAVAR-treated patients as compared to none of the placebo-treated patients. cause birth defects or fetal loss. Instruct both men and women of childbearing potential to use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Counsel female patients to contact their healthcare provider if they become pregnant while taking NEXAVAR. Hypocalcemia was more frequent and more severe in patients with DTC, especially those with a history of hypoparathyroidism, compared to patients with RCC or HCC. Hypocalcemia was observed in 36% of DTC patients receiving NEXAVAR (with 10% ≥ Grade 3) as compared When administered to rats and rabbits during the period of organogenesis, sorafenib was teratogenic and induced embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight). The effects occurred at doses considerably below the recommended buman dose of 400 mg twice daily (approximately 500 mg/m²/day on a body surface area basis). Adverse intrauterine development effects were seen at doses ≥ 0.2 mg/kg/day (1.2 mg/m²/day) in rats and 0.3 mg/kg/day (3.6 mg/m²/day) in rabbits. These doses result in exposures (AUC) approximately 0.008 times the AUC seen in patients at the recommended human dose. A NOAEL (no observed adverse effect level) was not defined for either species, since

9.2 Women of childbearing-potential In animals, sorafenib has been shown to be teratogenic and embryotoxic. Adequate contraception should be used during therapy and for at least 2 weeks after completion of therapy (see section WARNINGS AND PRECAUTIONS and PRECLINICAL SAFETY DATA).

It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NEXAVAR, a decision should be made whether to scontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. ing administration of radiolabeled sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma AUC ratio was approximately 5:1.

Results from animal studies indicate that sorafenib can impair male and female fertility (see section Preclinical safety data

The safety and effectiveness of NEXAVAR in pediatric patients have not been studied.

Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses \ge 600 mg/m² (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m²/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m²/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

EXAVAR were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some 9.7 Patients with Hepatic Impairmen

In total, 59% of HCC patients treated with NEXAVAR were age 65 years or older, and 19% were 75 and older. In total, 32% of RCC patients treated with

moderate (n=14) hepatic impairment compared to subjects (n=15) with normal hepatic function. No dose adjustment is necessary for patients with mild or oderate hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.2)]. 9.8 Patients with Renal Impairment

No correlation between sorafenib exposure and renal function was observed following administration of a single oral dose of NEXAVAR 400 mg to subjects with normal renal function and subjects with mild (CrCl 50–80 mL/min), moderate (CrCl 30–<50 mL/min), or severe (CrCl <30 mL/min) renal impairment who are not on dialysis. No dose adjustment is necessary for patients with mild, moderate or severe renal impairment who are not on dialysis. The pharmacokinetics of sorafenib have not been studied in patients who are on dialysis [see Clinical Pharmacology (12.2)].

Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised. here is no specific treatment for NEXAVAR overdose.

9.6 Geriatric Use

Not Known

The highest dose of NEXAVAR studied clinically is 800 mg twice daily. The adverse reactions observed at this dose were primarily diarrhea and dermatologic No information is available on symptoms of acute overdose in animals because of the saturation of absorption in oral acute foxicity studies conducted in

In cases of suspected overdose, NEXAVAR should be withheld and supportive care institute AVAR, a kinase inhibitor, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoro

phenyl]ureido}phenoxy)N₂-methylpyridine-2-carboxamide 4-methylbenzenesulfonate and its structural formula is

orafenib tosylate is a white to yellowish or brownish solid with a molecular formula of $C_{21}H_{16}CIF_3N_4O_3 \times C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400. Each red, round NEXAVAR film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients roscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, magnesium stearate, macrogol 3350, titanium dioxide and ferric

12.1 Mechanism of Action Sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Several of these kinases are thought to be involved in umor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth and angiogenesis of human hepatocellular carcinoma and renal cell

arcinoma, and several other human tumor xenografts in immunocompromised mice. Sorafenib also inhibited tumor growth of differentiated thyroid

12.2 Pharmacokinetics After administration of NEXAVAR tablets, the mean relative bioavailability is 38-49% when compared to an oral solution. The mean elimination half-life of afenib is approximately 25-48 hours. Multiple doses of NEXAVAR for 7 days resulted in a 2.5- to 7-fold accumulation compared to single dose. Steady-state plasma sorafenib concentrations are achieved within 7 days, with a peak-to-trough ratio of mean concentrations of less than 2. The steady-state concentrations of sorafenib following administration of 400 mg NEXAVAR twice daily were evaluated in DTC, RCC and HCC patients. Patients with DTC have mean steady-state concentrations that are 1.8-fold higher than patients with HCC and 2.3-fold higher than those with RCC. The reason for increased sorafenib concentrations in DTC patients is unknown

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When a moderate-fat meal (30% fat; 700 calories), bioavailability was similar to that in the fasted state. With a high-fat meal (50% fat; 900 calories), bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that NEXAVĂR be administered without food. [sée Dosage and Administration (2) Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily. In vitro binding of sorafenib to human plasma

Metabolism and Elimination Sorafenib is metabolized primarily in the liver undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib conjugates may be cleaved in the GI tract by bacterial glucuronidase activity, allowing reabsorption of unconjugated drug. Co-administration of neomycin interferes with this process, decreasing the mean bioavailability of sorafenib by 54%.

Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, or

in feces but not in urine. asians (N=40). Gender and age do not have a clinically meaningful effect on the pharmacokinetics of sorafenib

There are no pharmacokinetic data in pediatric patients.

12.3 Pharmacodynamics

Sorafenib is cleared primarily by the liver. In hepatocellular carcinoma (HCC) patients with Child-Pugh A or B (mild to moderate) hepatic impairment, exposure values were comparable and within the range observed in patients without hepatic impairment. The pharmacokinetics (PK) of sorafenib in Child-Pugh A and Child-Pugh B non-HCC patients were similar to the PK in healthy volunteers. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment [see Warnings and Precautions (6.11) and Use in Specific Populations (9.7)]. Renal Impairment

In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted 6.32 bicorease in doctaxel C_{max}. Caution is recommended when NEXAVAR is co-administered with docetaxel.

8.3 Doxorubicin/Irinotecan

8.3 Doxorubicin/Irinotecan

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8.5 Doxorubicin/Irinotecan

8.6 Doxorubicin/Irinotecan

8.6 Doxorubicin/Irinotecan

8.7 Doxorubicin/Irinotecan

8.8 Doxorubicin/Irinotecan

8.9 Dox or severe renal impairment not undergoing dialysis [see Use in Specific Populations (9.8)].

AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown. (see section Special warnings and In a clinical pharmacology study, QT/QTc measurements were recorded in 31 patients at baseline (pre-treatment) and post-treatment. After one 28-day treatment cycle, at the time of maximum concentration of sorafenib, QTcB was prolonged by 4 ±19 msec and QTcF by 9 ±18 msec, as compared to placebo nent at baseline. No subject showed a QTcB or QTcF >500 msec during the post-treatment ECG monitoring. (see Special warnings and precautions for

3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ability of sorafenib The preclinical safety profile of sorafenib was assessed in mice, rats, dogs and rabbits.

Repeat-dose toxicity studies revealed changes (degenerations and regenerations) in various organs at exposures below the anticipated clinical exposure (based on AUC comparisons) After repeated dosing to young and growing dogs effects on bone and teeth were observed at exposures below the clinical exposure. Changes consisted in lar thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate, and alterations of the dentin composition. Similar effects were not induced in adult dogs. Positive genotoxic effects were obtained for sorafenib in an in vitro mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Sorafenib was not genotoxic in the *in vitro*-Ames test (the material contained the intermediate at 0.34%)

and in an in vivo mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (< 0.15%), was positive for mutagenesis in an in vitro bacterial cell assay (Ames test). No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. An adverse effect on male and female fertility can however be expected because repeat-dose studies in animals have shown changes in male and female reproductive organs at exposures below the anticipated clinical exposure (based on AUC). Typical changes consisted of signs of degeneration and retardation in testes, epididymides, prostate, and

degeneration in the testes at 600 mg/m2/day,and oligospermia at 1200 mg/m2/day of sorafenib. Sorafenib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below the clinical exposure. Observed

The clinical safety and efficacy of NEXAVAR have been studied in patients with hepatocellular carcinoma (HCC), renal cell carcinoma (RCC) and

quate contraception should be used during therapy and for at least 2 weeks after completing therapy.

14.1 Hepatocellular Carcinoma

Administration (CYP2D8 substrate), and omeprazole (CYP2D9 substrate). The possible effect of bepaticular carcinoma. Overall survival was the pnmary enopoint. A local of or machining placebo.

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9 substrate warfarin was assessed indirectly by measuring PT-INR. The mean changes from baseline in PT-INR were not higher in NEXAVAR patients compared to placebo patients, suggesting that sorafenib did not inhibit warfarin metabolism in vivo and may not be an were not higher in NEXAVAR patients compared to placebo groups with regard to age, gender, race, performance in vivo inhibitor of CYP2C9. Isee Warnings and Precautions (6.7)].

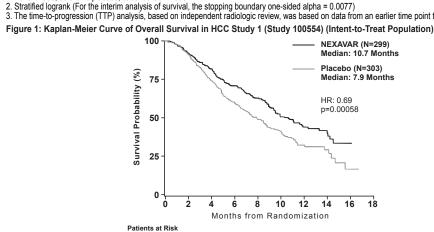
Demographics and baseline disease characteristics were similar between the NEXAVAR or placebo for a further 12 weeks. Patients who were permitted to vs. 43.6%; stage II: 10.4% vs. 8.3%; stage II: 10.4% vs. VS. 43.0%, Stage 14. 30.4% vs. 40.9%), absence to built marksoph are vascular invasion and extranepatic united specified (30.1% vs. 30.0%), and barcetona Clinic Liver Cancer stage (stage B: 18.1% vs. 16.8%; stage C: 81.6% vs. 83.2%; stage D: 41% vs. 0%). Liver impairment by Child-Pugh score was comparable between the NEXAVAR and placebo groups (Class A: 95% vs. 98%; B: 5% vs. 2%). Only one patient with Child-Pugh class C was entered. Prior treatments included surgical resection procedures (19.1% vs. 20.5%), locoregional therapies (including radiofrequency ablation, percutaneous ethanol injection and transarterial chemoembolization; 38.8% vs. 40.6%), radiotherapy (4.3% vs. 5.0%) and systemic therapy (3.0% vs. 5.0%) (see Table 9). The trial was stopped for efficacy following a pre-specified second interim analysis for survival showing a statistically significant advantage for NEXAVAR over placebo for overall survival (HR: 0.69, p= 0.00058) (see Table 10 and Figure 1). This advantage was consistent across all subsets analyzed. Final analysis of time to tumor progression (TTP) based on data from an earlier time point (by independent radiologic review) also was significantly longer in

14.3 Differentiated Thyroid Carcinoma

ild-Pugh Status n (%)			Placebo (n=303)	Sorafenib (n=299)
nu-rugii Status II (70)			297 (98%) 6 (2%) 0 (0%)	284 (95%) 14 (5%) 1 (0.3%)
patitis from Laboratory n (%) epatitis C only epatitis B only epatitis B & C egative serology for HCV Ab or H issing	IBs Ag		81 (27%) 28 (9%) 3 (1%) 165 (55%) 26 (9%)	86 (29%) 32 (11%) 7 (2%) 149 (50%) 25 (8%)
le 10 : Efficacy Results fror	n HCC Study 1 (Study 100	554)		
fficacy Parameter	Nexavar (N=200)	Placebo	Hazard Ratio ¹	P-value

patitis B & C pative serology for HCV Ab or F sing	HBs Ag		165 (55%) 26 (9%)	7 (2%) 149 (50%) 25 (8%)
10 : Efficacy Results from	m HCC Study 1 (Study 100	554)		
cacy Parameter	Nexavar (N=299)	Placebo (N=303)	Hazard Ratio ¹ (95% CI)	P-value (log rank test ²)
rall survival				
lian, months	10.7	7.9	0.69	0.00058
% CI)	(9.4, 13.3)	(6.8, 9.1)	(0.55, 0.87)	
of events	143	178		
e to Progression ³				
lian, months	5.5	2.8	0.58	0.000007
% CI)	(4.1, 6.9)	(2.7, 3.9)	(0.45, 0.74)	
Of events	107	156		
nfidence interval	'	•	1	

Hazard ratio, sorafenib/placebo, stratified Cox model Stratified logrank (For the interim analysis of survival, the stopping boundary one-sided alpha = 0.0077) The time-to-progression (TTP) analysis, based on independent radiologic review, was based on data from an earlier time point than the survival analysis



Placebo 272 217 174 108 69 31 14 3 In a trial of HCC patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, the systemic exposure (AUC) of sorafenib was within the range observed in patients without hepatic impairment. In another trial in subjects without HCC, the mean AUC was similar for subjects with mild (n=15) and shorter for sorafenib than placebo (47 days vs. 84 days), the median OS (257 days vs. 171 days) and TTP (126 days vs. 80 days) were longer for sorafenib than placebo which both OS and TTP were the most important endpoints after treatment (see Table 11). From the published paper of Albou-Alfa, Child-Pugh B patients treated with NEXAVAR have more cases of hyperbilirubinemia, encephalopathy and ascites. Please refer to the references for details. (G. K. Albou-Alfa et al. Is sorafenib safe and effective in patients with hepatocellular carcined (HCC) and Child-Pugh B (CPB) cirrhosis? Journal of Clinical Oncology. 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 26, No 15S (May 20 Supplement) 2008: 4518.

·	Placebo (n=73)	Sorafenib (n=95)
Baseline Characteristics	(- /	(/
Child-Pugh Status, (n)		
A	72	85
B	1	10
Etiology, (n)	•	
Alcohol	17	31
Hepatitis B only	12	14
Hepatitis C only	19	26
Others	11	8
Unknown	14	16
Number reached Child-Pugh B, (n)	71	88
Number reached Child-Pugh C, (n)	2	7
Median time to Child-Pugh B or C measured from baseline	84 days	47 days
Median time on treatment after achieving status Child-Pugh B or C	22 days	48 days
Median OS in these subjects	171 days	257 days
TTP (based on independent review)	80 days	126 days
6-month OS rate	46%	62%
Radiological progression-free rate at 3 months	38%	60%
Radiological progression-free rate at 6 months	13%	41%

randomized to placebo and 150 subjects were randomized to NEXAVAR. Analysis of efficacy data revealed that NEXAVAR significantly prolonged OS compared with placebo (HR: 0.68, p= 0.014). The analysis of TTP also reveals a significant and meaningful improvement in growment in growment in maximum provided by the subjects compared to 84 days for NEXAVAR an increase the risk of bleeding and that they should promptly report any episodes of bleeding.

Inform patients that NEXAVAR can increase the risk of bleeding and that they should promptly report any episodes of bleeding.

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Table 12: Efficacy Results from HCC study 2 (study 11849)

ble 12. Efficacy Results from Hoc study 2 (study	y 1104 <i>3)</i>			
fficacy Parameter	Nexavar	Placebo	P-value	HR
•	(N=150)	(N=76)		(95% CI)
verall survival (OS)	198	127	0.014	0.68
nedian, days (95% CI)]	(169, 230)	(114, 166)	0.014	(0.50, 0.93)
me to Progression, (TTP)	84	41.5	< 0.001	0.57
nedian, days (95% CI)]**	(80, 109)	(41, 47)	0.001	(0.42, 0.79)
: Confidence interval, HR= Hazard ratio (NEXAVAR over place	bo)			
2 Banal Call Carainama				

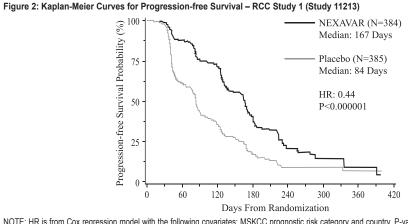
he safety and efficacy of NEXAVAR in the treatment of advanced renal cell carcinoma (RCC) were studied in the following two randomized controlled clinical RCC Study 1 (Study 11213) was a Phase 3, international, multicenter, randomized, double blind, placebo-controlled trial in patients with advanced renal cell carcinoma who had received one prior systemic therapy. Primary study endpoints included overall survival and progression-free survival (PFS). Tumor response rate was a secondary endpoint. The PFS analysis included 769 patients stratified by MKCC (Memorial Sloan Kettering Cancer Center) prognostic risk category (low or intermediate) and country and randomized to NEXAVAR 400 mg twice daily (N=384) or to placebo (N=385) Table 13 summarizes the demographic and disease characteristics of the study population analyzed. Baseline demographics and disease characteristics

were well balanced for both treatment groups. The median time from initial diagnosis of RCC to randomization was 1.6 and 1.9 years for the NEXAVAR and

Table 13 : Demographic and Disease Characteristics – RCC Study 1 (Study 11213) Characteristics NEXAVAR N=384 Placebo N=385

Black/Asian/Hispanic/Other	11	(3)	10	(2)
Not reported ^a	97	(25)	97	(25)
Age group				
<65	255	(67)	280	(73)
≧65	127	(33)	103	(27)
ECOG performance status at baseline				
0	184	(48)	180	(47)
1	191	(50)	201	(52)
2	6	(2)	1	(< 1)
Not reported	3	(< 1)	3	(< 1)
MSKCC prognostic risk category				
Low	200	(52)	194	(50)
Intermediate	184	(48)	191	(50)
Prior IL-2 and/or interferon				
Yes	319	(83)	313	(81)
No	65	(17)	72	(19)

a. Race was not collected from the 186 patients enrolled in France due to local regulations. In 8 other patients, race was not available at the time of analysis.



seminal vesicles of rats. Female rats showed central necrosis of the corpora lutea and arrested follicular development in the ovaries. Dogs showed tubular degeneration in the testes at 600 mg/m2/day,and oligospermia at 1200 mg/m2/day,and oligospermia at 1200 mg/m2/day,and oligospermia at 1200 mg/m2/day,and oligospermia at 1200 mg/m2/day. The median PFS for patients randomized to NEXAVAR was 167 days compared to 84 days for patients randomized to placebo. The estimated hazard ratio (risk of progression with NEXAVAR compared to placebo) was 0.44 (95% CI: 0.35, 0.55).

A series of patient subsets were examined in exploratory univariate analyses of PFS. The subsets included age above or below 65 years, ECOG PS 0 or 1 effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions and an increased number of external and visceral malformations.

Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

MSKCC prognostic risk category, whether the prior therapy was for progressive metastatic disease or for an earlier disease setting, and time from diagnosis of less than or greater than 1.5 years. The effect of NEXAVAR on PFS was consistent across these subsets, including patients with no prior IL-2 or interferon therapy (n=137; 65 patients receiving NEXAVAR and 72 placebo), for whom the median PFS was 172 days on NEXAVAR compared to 85 days on placebo. mor response was determined by independent radiological review according to RECIST criteria. Overall, of 672 patients who were evaluable for response, (2%) NEXAVAR patients and 0 (0%) placebo patients had a confirmed partial response. Thus the gain in PFS in NEXAVAR-treated patients primarily At the time of a planned interim survival analysis, based on 220 deaths, overall survival was longer for NEXAVAR than placebo with a hazard ratio (NEXAVAR

patients were randomized to NEXAVAR or placebo. After an additional 12 weeks, at week 24, for the 65 randomized patients, the progression-free rate was significantly higher in patients randomized to NEXAVAR (16/32, 50%) than in patients randomized to placebo (6/33, 18%) (p=0.0077). Progression-free survival was significantly longer in the NEXAVAR group (163 days) than in the placebo group (41 days) (p=0.0001, HR=0.29). The safety and effectiveness of NEXAVAR was established in a multicenter, randomized (1:1), double-blind, placebo-controlled trial conducted in 417 patients with locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) réfractory to radioactive iodine (RAI) treatment. Randomization was stratified by age (< 60 years versus ≥ 60 years) and geographical region (North America, Europe, and Asia).

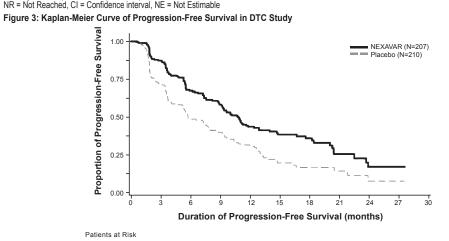
All patients were required to have actively progressing disease defined as progression within 14 months of enrollment. RAI-refractory disease was defined based on four criteria that were not mutually exclusive. All RAI treatments and diagnostic scans were to be performed under conditions of a low iodine diet and adequate TSH stimulation. Following are the RAI-refractory criteria and the proportion of patients in the study that met each one: a target lesion with no iodine uptake on RAI scan (68%); tumors with iodine uptake and multiple RAI treatments with the last treatment greater than 16 months prior to enrollment, and disease progression after each of two RAI treatments administered within 16 months of each other (7%); cumulative RAI dose 2 600 mCi administered (34%). The major efficacy outcome measure was progression-free survival (PFS) as determined by a blinded, independent radiological review using a modified Response Evaluation Criteria in Solid Tumors v. 1.0 (RECIST). RECIST was modified by inclusion of clinical progression of bone lesions based on the need for external beam radiation (4.4% of progression events). Additional efficacy outcomes measures included overall survival (SS), tumor reproses rate, and duration of response. progression events). Additional efficacy outcomes measures included overall survival (OS), tumor response rate, and duration of response. Patients were randomized to receive NEXAVAR 400 mg twice daily (n=207) or placebo (n=210). Of the 417 patients randomized, 48% were male, the media age was 63 years, 61% were 60 years or older, 60% were white, 62% had an ECOG performance status of 0, and 99% had undergone thyroidectomy. The histological diagnoses were papillary carcinoma in 57%, follicular carcinoma (including Hürthle cell) in 25%, and poorly differentiated carcinoma in 10%, and

other in 8% of the study population. Metastases were present in 96% of the patients: lungs in 86%, lymph nodes in 51%, and bone in 27%. The mediar cumulative RAI activity administered prior to study entry was 400 mCi. A statistically significant prolongation in PFS was demonstrated among NEXAVAR-treated patients compared to those receiving placebo. Following investigator-determined disease progression, 157 (75%) patients randomized to placebo crossed over to open-label NEXAVAR, and 61 (30%) patients randomized to NEXAVAR received open-label NEXAVAR. There was no statistically significant difference in overall survival between the two treatment arms

	NEXAVAR N=207	Placebo N=210
Progression-free Survival 1		
lumber of Deaths or Progression	113 (55%)	136 (65%)
Median PFS in Months (95% CI)	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)
Hazard Ratio (95% CI)	0.59 (0.4	46, 0.76)
P-value ²	<0.	001
Overall Survival ³		
lumber of Deaths	66 (32%)	72 (34%)
Median OS in Months (95% CI)	NR	36.5 (32.2, NR)
lazard Ratio (95% CI)	0.88 (0.6	53, 1.24)
P-value ²	0.	47
Objective Response		
Number of Objective Responders ⁴	24 (12%)	1 (0.5%)
95%CI)	(7.6%, 16.8%)	(0.01%, 2.7%)
Median Duration of Response in Months (95% CI)	10.2 (7.4, 16.6)	NE

2 Two-sided log-rank test stratified by age (< 60 years, ≥ 60 years) and geographic region (North America, Europe, Asia) cted 9 months after the data cut-off for the final PFS analy

4 All objective responses were partial responses NR = Not Reached, CI = Confidence interval, NE = Not Estimable



NEXAVAR 207 159 115 91 60 35 27 13 5 2 Placebo 210 135 78 55 36 14 9 6 2 2 15 HOW SUPPLIED/STORAGE AND HANDLING VEXAVAR tablets are supplied as round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side, each

Tablet core: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate magnesium stearate. Film-coat: hypromellose, macrogol3350, titanium dioxide, iron oxide red.

8-1000 tablets Aluminum blister per box

Store below 30°C in a dry place. Keep out of the reach of childre 16 PATIENT COUNSELING INFORMATION 16.1 Cardiac Ischemia; Infarction

Discuss with patients that cardiac ischemia and/or infarction has been reported during NEXAVAR treatment, and that they should immediately report any episodes of chest pain or other symptoms of cardiac ischemia and/or infarction [see Warnings and Precautions (6.1)].

Inform patients that bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR and that their INR should be monitored regularly [see Warnings and Precautions (6.7)].

Inform patients that hypertension can develop during NEXAVAR treatment, especially during the first six weeks of therapy, and that blood pressure should be monitored regularly during treatment. [See Warnings and Precautions (6.4 and 6.5)] 16.4 Skin Reactions Advise patients of the possible occurrence of hand-foot skin reaction and rash during NEXAVAR treatment and appropriate countermeasures.

16.5 Gastrointestinal Perforation Advise patients that cases of gastrointestinal perforation have been reported in patients taking NEXAVAR [see Warnings and Precautions (6.3 and 6.6)]. 16.6 Wound Healing Complications

Inform patients that temporary interruption of NEXAVAR is recommended in patients undergoing major surgical procedures [see Warnings and Precautions

Inform patients that NEXAVAR can cause birth defects or fetal loss. Counsel both male and female patients to use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment.

Inform female patients to contact their healthcare provider if they become pregnant while taking NEXAVAR [see Warnings and Precautions (6.10), Use in Specific Populations (9.1)1. 16.9 Nursing Mothers Advise mothers not to breast-feed while taking NEXAVAR [see Use in Specific Populations (9.3)]. 16.10 Missed Doses

Instruct patients that if a dose of NEXAVAR is missed, to take the next dose at the regularly scheduled time, and not double the dose. Instruct patients to contact their healthcare provider immediately if they take too much NEXAVAR. Bayer AG, Kaiser-Wilhelm-Allee, 51368 Leverkusen, German NEXAVAR film-coated tablets 200mg / USPI_11/2013 + CCDS21_12Jun2013/TW11

PMR 86316617 Technical Template (O8/00-N) Pantone: Black, 2718 514x910-16871