

爾必得舒® 注射液 5毫克/毫升

Erbitux® 5mg/ml solution for infusion

本藥限由醫師使用
衛署衛疫輸字第000877號

有效成分：Cetuximab

組成
每毫升的輸注溶液含有5毫克Cetuximab。每藥瓶含20毫升。
賦形劑：氯化鈉 (sodium chloride)、glycine、polysorbate 80、citric acid monohydrate、氫氧化鈉(sodium hydroxide)和注射用水。

特性
作用機理
表皮生長因子受體 (Epidermal Growth Factor Receptor) 是與控制細胞存活、細胞週期變化、血管生成、細胞移動和細胞侵入/轉移等有關的訊號途徑的一份子。Cetuximab是一種直接對抗表皮生長因子受體的嵌合 (chimeric) 型單株IgG1抗體。它對受體的親合力比內生性連結物 (Ligand) 約高5至10倍，因而可以阻斷受體的功能。它能誘發表皮生長因子受體的內在化作用 (internalization)，可能因而造成表皮生長因子受體的負向調控 (down-regulation)。Cetuximab也可作用於細胞毒性免疫效應細胞而對那些具有表皮生長因子腫瘤細胞產生作用 (抗體依賴型的細胞媒介細胞毒性作用 (antibody dependent cell-mediated cytotoxicity))。Cetuximab不與HER的受體結合。

藥效學作用
Cetuximab抑制那些具表皮生長因子受體表現型的人類腫瘤細胞的生長，以及誘發細胞的死亡 (apoptosis)。它也會抑制血管生成因子的產生、阻止內皮細胞移動，因而減少腫瘤的新血管生成及轉移。

直腸結腸癌
Cetuximab和irinotecan合併使用的二項臨床試驗，總共研究356位接受過含irinotecan的細胞毒性治療失敗而接受Cetuximab和irinotecan合併使用治療的具表皮生長因子受體表現型的轉移性結腸直腸癌的患者。於腫瘤檢測中使用一種診斷試劑 (EGFR pharmDx™) 進行免疫組織化學檢測表皮生長因子受體在腫瘤的表現。對結腸直腸癌轉移的患者的臨床試驗評估中，大約75%是具有表皮生長因子受體表現型的腫瘤，因此這些患者被認為符合Cetuximab治療的標準。
治療結果摘要如下：

研究	人數	ORR		DCR		TTP (月)		OS (月)	
		人數 (%)	95%	人數 (%)	95%	中數	95%	中數	95%
合併治療									
EMR 62 202-007	218	50(22.9)	17.5, 29.1	121(55.5)	48.6, 62.2	4.1	2.8, 4.3	8.6	7.6, 9.6
IMCL CP02-9923	138	21(15.2)	9.7, 22.3	84(60.9)	52.2, 69.1	2.9	2.6, 4.1	8.4	7.2, 10.3
單一治療*									
EMR 62 202-007	111	12(10.8)	5.7, 18.1	36(32.4)	23.9, 42.0	1.5	1.4, 2.0	6.9	5.6, 9.1

*尚未核准
CI = 信賴區間 DCR = 疾病控制率 (完全反應、部分反應或穩定疾病之患者)
ORR = 客觀反應率 (完全反應、部分反應之患者)
OS = 存活期 TTP = 疾病開始惡化的時間

Cetuximab與irinotecan合併治療的效果比Cetuximab單一治療的效果要好，尤其是客觀反應率、疾病控制率和疾病開始惡化的時間等方面。

頭頸部鱗狀細胞癌
超過90%的頭頸鱗狀細胞癌患者其腫瘤具表皮生長因子受體表現型，因此，表皮生長因子受體表現型之免疫組織化學偵測未執行。
Cetuximab與放射線療法合併使用，治療局部晚期之口咽癌、下咽癌及喉癌患者。
EMR 62 202-006：此隨機分配臨床試驗，比較Cetuximab合併放射線治療 (211位患者) 及放射線單一治療 (213位患者) 在局部晚期之口咽癌、下咽癌及喉癌患者。Cetuximab於放射線治療前一週開始投予，並持續使用至放射線治療之療程結束。
治療結果摘要如下：

變數/統計	放射線治療 +Cetuximab	放射線單一治療
	(人數=211)	(人數=213)
局部控制		
月，中數 (95%CI)	24.4(15.7, 45.1)	14.9(11.8, 19.9)
Hazard比 (95%CI)	0.68 (0.52, 0.89)	
p-值	0.005	
存活期		
月，中數 (95%CI)	49.0(32.8, 62.6+)	29.3(20.6, 42.8)
Hazard比(95%CI)	0.74 (0.56, 0.97)	
p-值	0.032	

CI=confidence interval信賴區間，OS=存活期，“+”表示中斷時尚未到達上限值

患者預後結果依據腫瘤的程度作判定，當Cetuximab與放射線療法一起使用時，利用Karnofsky performance status (KPS)與年齡評估有較明顯的助益。患者年齡65歲或以上者，且KPS≤80者，無法證明具臨床效益。
Cetuximab與化學、放射線療法合併使用至目前並無深入之研究，因此，臨床效益-風險評估尚未建立。
Cetuximab與內含platinum類之化學療法合併使用，治療復發及/或轉移性頭頸部鱗狀細胞癌患者。
EMR 62 202-002：此隨機分配臨床試驗，針對先前從未接受過化學療法之復發及/或轉移性頭頸部鱗狀細胞癌患者，Cetuximab與cisplatin/carboplatin加上5-fluorouracil之合併治療 (222位患者) 和僅接受相同之化學療法 (220位患者) 相比較，Cetuximab與內含platinum類之化學療法合併使用至6個週期的療程後，持續使用Cetuximab直至病情惡化。
其治療結果摘要如下：

變數/統計	Cetuximab+化學療法	化學療法
	(人數=222)	(人數=220)
存活期		
月，中數 (95%CI)	10.1(8.6, 11.2)	7.4(6.4, 8.3)
Hazard比 (95%CI)	0.797 (0.644, 0.986)	
p-值	0.0362	
疾病無惡化存活期		
月，中數 (95%CI)	5.6(5.0, 6.0)	3.3(2.9,4.3)
Hazard比 (95%CI)	0.538(0.431,0.672)	
p-值	<0.0001	
客觀反應率		
百分比 (95%CI)	35.6(29.3, 42.3)	19.5(14.5,25.4)
p-值	0.0001	



CI=confidence interval信賴區間，CTX=內含platinum類之化學療法，ORR=客觀反應率，OS=存活期，PFS=疾病無惡化存活期

患者預後結果依據腫瘤的程度作判定，當Cetuximab與內含platinum類之化學療法合併使用時，利用Karnofsky performance status (KPS)與年齡評估有較明顯的助益。相對於疾病無惡化存活期，患者年齡65歲或以上者，且KPS≤80者在存活期無法證明具臨床效益。

免疫生成反應
產生人類抗嵌合抗體 (HACA) 是單株嵌合型抗體的一種專一效果。所研究的患者中，3.4%出現可以測量到的人類抗嵌合抗體 (HACA) 滴定量。並沒有觀察到對Cetuximab的中和作用。人類抗嵌合抗體 (HACA) 的出現與Cetuximab造成的過敏反應或任何其他不良反應發生無關。

藥物動力學特性
靜脈輸注的Cetuximab，當每星期的劑量在體表面積5至500毫克/米²之間時，具有劑量依賴性藥物動力反應。當給予Cetuximab初始劑量400毫克/米²體表面積時，其平均分布容積約相當於血液的體積 (2.9升/米²體表面積，範圍從1.5到6.2升/米²體表面積)。平均最高濃度Cmax (±標準差) 是185±55微克/毫升。平均清除率為0.022升/小時 每米²體表面積。Cetuximab的排泄半衰期很長，治療劑量下的範圍從70至100小時。Cetuximab血清濃度於單一治療三星期後，才會達到穩定濃度。第三星期時，Cetuximab平均最高濃度為155.8微克/毫升，第8星期時是151.6微克/毫升，而相對的最低濃度分別是41.3和55.4微克/毫升。一項Cetuximab和irinotecan合併治療的研究顯示，Cetuximab的平均最低濃度，第12星期時是50.0微克/毫升，第36星期時是49.4微克/毫升。有幾種可能是抗體代謝的途徑曾經被提出。所有這些途徑都是將抗體生物分解成較小的分子。一項綜合所有臨床研究的整合分析顯示，Cetuximab的藥物動力特性不會受種族、年紀、性別、腎臟或肝臟狀況的影響。

非臨床的安全性數據
劑量依賴性皮膚病變 (dose-dependent skin alteration) 是在動物毒性試驗最主要的發現，主要開始出現在其劑量使用等於人類用量時。在恆河猴的胚胎-胎兒毒性研究顯示，並無致畸胎性；然而觀察到依據其劑量之增加而增加流產機率。對基因毒性和包括非主要注射途徑造成的局部耐受性的非臨床研究數據顯示對人類並無特別的危害。沒有進行過正式的動物研究來確定Cetuximab致癌的可能性，以及檢測其對男性或女性生育的影響。尚無Cetuximab和化學療法藥品合併治療的毒性研究。目前還沒有Cetuximab對傷口癒合影響的非臨床資料。然而，在臨床前期傷口癒合模型中，表皮生長因子受體的選擇性酪胺酸激酶 (tyrosine kinase) 抑制劑顯示會延緩傷口癒合。

適應症
Erbitux與irinotecan合併使用，治療經內含irinotecan之細胞毒性治療失敗且具有表皮生長因子受體表現型的轉移性直腸結腸癌病患。
Erbitux與放射線療法合併使用，治療局部晚期之口咽癌、下咽癌及喉癌患者。
Erbitux與內含platinum類之化學療法合併使用，治療復發及/或轉移性頭頸部鱗狀細胞癌患者。

禁忌症

Erbitux禁用於已知對Cetuximab有嚴重過敏反應的患者 (第3或4級；美國國家癌症機構一般毒性標準，NCI-CTC)。
在使用合併療法治療前，需考慮伴隨使用的化學療法藥品或放射線治療之禁忌症。

懷孕和哺乳
表皮生長因子受體和胎兒的發育有關。在有限的動物研究觀察發現Cetuximab及其他免疫球蛋白G1 (IgG1) 抗體能夠通過胎盤的障壁。動物實驗數據顯示目前無致畸胎情形，然而，隨著劑量增加，流產發生的機率相對增加。目前還沒有足夠的孕婦使用數據。強烈建議，只有當可能的效益超過對胎兒的可能危險性時，才可以給予孕婦或沒有適當避孕措施的婦女使用Erbitux。建議，在Erbitux治療期間和最後一劑治療後的二個月內的婦女，不要哺餵母乳，因為尚未知Erbitux是否會從母乳排出。

特殊警語和注意事項

輸注相關反應

若患者出現輕度到中度輸注相關的反應，可能要降低輸注速率。建議之後繼續保持這種較低的輸注速率。
使用Erbitux治療產生之嚴重的輸注相關的反應已被報告過，症狀的發生通常是在第一次輸注及輸注結束後一小時內，但也可能發生於數小時後。建議提醒患者有這一種延緩作用的可能，同時要指示患者如果發生輸注相關反應，要聯絡他們的醫師。如果發生嚴重輸注相關反應，要立即且永遠終止Erbitux的治療，可能還需要緊急治療。
建議對於表現狀況變差和本來就有心肺疾病的患者，要特別小心。

呼吸失調

Erbitux引起關係不明的間質性肺部功能異常的個案也曾被報告。如果經診斷為間質性肺部疾病，需停止使用Erbitux並且給予患者適當的治療。

皮膚反應

如果患者出現嚴重皮膚反應 (第3級；美國國家癌症機構一般毒性標準)，必需中斷Erbitux治療。只有在反應減輕成第2級時，才可恢復治療。
如果第一次使用時就出現嚴重的皮膚反應，在重新開始治療時無需調整其劑量。
發生第二次和第三次嚴重皮膚反應時，要再度中斷Erbitux治療。只有在反應減輕成第2級時，才可以較低劑量重新開始治療 (第二次發作：200mg/m²體表面積，第三次發作：150mg/m²體表面積)。
如果發生第四次嚴重皮膚反應，或中斷治療期間症狀沒有減輕成第2級，要永遠終止Erbitux治療。

電解質失調

常發生血清鎂的含量逐漸減少，可能引發嚴重的低血鎂症，其在停用Erbitux之後是可恢復的。此外，因腹瀉所導致的低血鉀症也可能發生。低血鈣也有可能會發生，特別是和內含platinum類之化學療法合併使用，嚴重低血鈣發生的頻率可能會增加。
建議於使用Erbitux治療前及治療期間監測患者的血清電解質，並於必要時做適當的補充。

嗜中性白血球減少和相關感染引發的併發症

患者使用Cetuximab與內含platinum類之化學療法合併使用時，可能會增加嚴重嗜中性白血球減少的風險，及其隨之而來的感染併發症，譬如發熱性嗜中性白血球減少、肺炎及敗血症。特別針對曾經有皮膚機能損害、黏膜炎或腹瀉情形的此類患者建議需嚴密監測，因為這些情形會增加感染的發生。

合併治療

關於化學療法藥品的其它警語和注意事項，請參閱其產品資訊。
Cetuximab合併放射線治療直腸結腸癌的經驗是有限的。

對開車和操作機器能力的影響

目前並無對開車和操作機器能力影響的研究。如果患者有治療相關症狀影響到自己的注意力集中和反應能力時，建議他們在此影響消失前，不要開車或使用機器。

特殊族群

截至目前為止，只有對有適當腎功能和肝功能的患者進行過研究 (不超過正常範圍上限值：血清肌酸酐≤1.5倍，轉胺酶≤5倍，膽紅素≤1.5倍)。
Erbitux未曾在患有下列一種或多種檢驗室項目異常的患者進行過研究：
血紅素<9克/分升、白血球計數<3000/毫米³、絕對嗜中性白血球計數<1,500/毫米³、血小板計數<100,000/毫米³。
Erbitux用於小兒科患者的安全性和效益尚未確定。
老年人不需要劑量調整，但使用於75歲及以上患者的經驗是有限的。

不良反應

下列不良反應可能於使用Erbitux治療時發生：

定義不良反應發生率的頻率，常用術語如下：

非常常見 (≥ 1/10)
常見 (≥ 1/100至<1/10)
不常見 (≥ 1/1,000至<1/100)

神經系統障礙

常見：頭痛

視覺障礙

常見：結膜炎

不常見：睪丸炎、角膜炎

呼吸、胸腔及橫膈障礙

不常見：肺栓塞

胃腸障礙

常見：腹瀉、噁心、嘔吐

皮膚及皮下組織障礙

非常常見：皮膚反應*

頻率不明：皮膚損傷處的重覆感染

罕見 (≥ 1/10,000至<1/1,000)

非常罕見 (<1/10,000)

頻率不明 (無法從現有的數據中預估) “*” 是代表對其副作用有詳細說明

代謝及營養障礙

非常常見：低血鎂症

常見：脫水，特別是續發性腹瀉或黏膜炎；低血鈣症；厭食所導致的體重減輕

血管障礙

不常見：深部靜脈血栓

全身性障礙及注射部位反應

非常常見：輕到中度輸注相關反應*、輕到中度黏膜炎可能導致之鼻出血

常見：嚴重輸注相關反應*、疲勞

肝膽障礙：

非常常見：肝臟酵素植增加 (ASAT、ALAT、AP)

CH0016

詳細說明

整體而言，在臨床上的反應並不因性別而有所差異。

輸注相關反應：

常見的輕度到中度輸注相關反應包含發燒、寒顫、暈眩或呼吸困難等症狀，在第一次輸注Erbitux時曾短暫出現。嚴重的輸注相關反應可能會發生，極少數的案例可能死亡。他們通常在第一次輸注Erbitux期間或一個小時內發生，但也可能發生在數小時後或後續輸注中。雖然潛在性的原因還無法被確認，但部份的反應為自然發生的偽過敏/過敏反應，可能的症狀包括支氣管痙攣、蕁麻疹、血壓增加或減少、失去意識或休克。在罕見的個案中，曾發現狹心症、心肌梗塞或心跳停止。

關於輸注相關反應的臨床處理，請見“警語及注意事項”。

皮膚反應：

超過80%的患者可能出現皮膚反應，主要呈現痤瘡狀紅疹，和/或較少發生的瘙癢、皮膚乾燥、皮膚脫屑、多毛症或指甲病變(例如甲溝炎)。這些反應大約有15%是嚴重的，包括皮膚壞疽的單獨個例。皮膚反應主要出現在治療的前三個星期，只要是在建議劑量下，依指示中斷治療，皮膚反應總是能緩解，且沒有後遺症。依據NCI-CTC第二級皮膚反應的特徵為超過一半的體表面積出現紅疹，第三級則是超過一半以上的體表面積出現紅疹。

Erbitux對皮膚的損害使患者易受感染(如金黃色葡萄球菌)，可能造成併發症如蜂窩性組織炎、丹毒、或潛在性致死、葡萄球菌脫皮症狀或敗血症。

合併治療

當Erbitux與其他化學療法藥品合併使用時，請分別參閱其產品訊息。

和化學療法藥品合併使用的副作用請見“藥物交互作用”。

合併局部放射線療法用以治療頭頸部位，常見傳統放射線療法的不良反應(如黏膜炎、放射線皮膚炎、吞嚥困難或白血球減少，較常見者為淋巴球減少)。在一424位患者參與之隨機分配對照的臨床研究，Erbitux與放射線療法合併使用較單一放射線療法治療的組別有輕微較高的不良反應發生率在急性嚴重放射線皮膚炎、黏膜炎及放射線療法後之相關症狀。

交互作用

與內含platinum類之化學療法合併使用時，嚴重白血球減少或中性白血球減少，及其隨之而來的感染併發症，譬如發熱性嗜中性白血球減少，肺炎及敗血症的發生頻率較僅接受相同之platinum類化學療法使用時可能會增加（請見特殊警語及注意事項）。

與5-fluorouracil合併使用時，心臟局部缺血的症狀包括心肌梗塞、充血性心臟衰竭及手足症候群（手足皮膚紅斑、感覺異常）的發生頻率較5-fluorouracil單一使用時為增加。

一項正式臨床研究，其與irinotecan的交互作用顯示這兩種藥物合併使用時，它們各自的藥物動力作用都沒有改變。臨床數據顯示，對Erbitux的整體安全性沒有影響。目前沒有Erbitux與其他交互作用的正式臨床研究。

劑量和使用方式

Erbitux必須在有抗腫瘤藥物製品使用經驗的醫師監督下才能使用。輸注期間和輸注結束後一小時內都要密切觀察患者。一定要備妥急救設備。

患者第一次輸注前，一定要先給予抗組織胺藥劑及皮質類固醇。並建議之後的每一次注射都要先給予抗組織胺藥劑及皮質類固醇。

在治療上，Erbitux為一星期輸注一次，起始劑量是每平方公尺體表面積400毫克(400 mg/m²)建議的輸注時間是120分鐘。之後每一星期的劑量是每平方公尺體表面積250毫克(250 mg/m²)建議的輸注時間是60分鐘。Erbitux最快的輸注速率不能超過10毫克/分。

直腸結腸癌

Erbitux與irinotecan合併使用，治療轉移之直腸結腸癌患者。合併使用irinotecan的劑量，請參閱其相關之個別產品資訊，一般狀況下，合併使用irinotecan的治療劑量，可投予最近治療療程相同劑量的irinotecan。必須在輸注Erbitux一小時之後，才能給予irinotecan。

建議持續Erbitux治療直至病情惡化。

頭頸部鱗狀細胞癌

Erbitux與放射線療法合併使用，治療局部晚期之口咽癌、下咽癌及喉癌患者建議在接受放射線療法的前一週開始Erbitux的治療且持續使用Erbitux治療至放射線治療期結束。

Erbitux與內含platinum類之化學療法合併使用，治療復發及/或轉移性頭頸部鱗狀細胞癌患者，必須在輸注Erbitux一小時之後，才能給予platinum類之化學療法。建議持續Erbitux治療直至病情惡化。

使用和配製指引

使用輸注幫浦、或重力滴下、或針筒幫浦進行靜脈輸注Erbitux 5毫克/毫升。輸注時一定要單獨使用一條管線，輸注結束時一定要用無菌的注射用9毫克/毫升（0.9％）氯化鈉溶液沖洗管線。Erbitux 5毫克/毫升是一種無色的溶液。

Erbitux 5毫克/毫升與下列材料相容：

- 聚乙烯（polyethylene，PE）、乙基乙酸乙烯酯（ethyl vinyl acetate，EVA）、或聚氯乙烯（polyvinyl chloride，PVC）質料的袋子。
- PE、EVA、PVC、TP (Polyolefine thermoplast) 或聚胺甲酸乙脂（polyurethane，PUR）質料的注射組件。
- 聚丙烯 (Polypropylene，PP) 質料用於針筒幫浦所使用的注射器。

Erbitux不含有任何抗菌的防腐劑或抑制細菌的藥劑。因此，準備輸注時一定要確保無菌操作。我們強烈建議，打開後要立即使用。

Erbitux 5毫克/毫升一定要遵照下列方式準備：

使用輸注幫浦或重力滴下法給藥（以9毫克/毫升(0.9%)的滅菌氯化鈉溶液稀釋）：取一足夠量的0.9%滅菌氯化鈉溶液輸注袋，計算Erbitux所需的量，將適量的氯化鈉溶液自輸注袋內移除。準備適當的無菌針筒，接上適當的針頭，從藥瓶中抽出Erbitux的需要量。將Erbitux移入準備好的無菌的輸注袋內。重複這一步驟直到達到所計算的數量。然後接上輸注管線及已備妥經稀釋的Erbitux。輸注時使用重力滴下法或輸注幫浦。依照上面的說明設定和控制速率。

使用輸注幫浦或重力滴下法給藥（未經稀釋）：計算Erbitux所需的量，取適當的無菌注射器（最小50毫升），並接上適當的針頭，從藥瓶中抽取Erbitux的需要量，將Erbitux移入一個無菌的空容器或袋子內，重複這一步驟直到達到所計算的數量。然後接上輸注管線及備妥的Erbitux。輸注時使用重力滴下法或輸注幫浦。依照上面的說明設定和控制速率。

以針筒幫浦給藥：拿一支適當的無菌針筒，接上適當的針頭。從藥瓶中抽取Erbitux的需要量。拔掉針頭，將針筒接到針筒幫浦。將注射管線連接到針筒上，依照上面的說明設定和控制速率，使用Erbitux或已滅菌之9毫克/毫升(0.9%)氯化鈉溶液灌注後開始輸注。若有需要，重複這一步驟直到達所計算的輸注量。

不相容性

Erbitux 5毫克/毫升絕對不能和其他靜脈注射藥物製品混合（除了“使用和配製指引”所提到的之外），一定要分別使用不同的輸注管線。

藥物過量

目前使用單一劑量高於每平方公尺體表面積400毫克，或每週給予高於每平方公尺體表面積250毫克的使用經驗尚有限。

保存和安定性

保存在冰箱（2°C–8°C）。不能冷凍。

超過使用期限不能使用。

請將藥物放在兒童拿不到的地方。

Erbitux 5毫克/毫升溶液若依上述方法配製，使用中的化學和物理安定性在25°C下維持48小時。Erbitux不含有任何抗菌的防腐劑或抑制細菌的藥劑。打開後要立即使用。如果沒有立即使用，使用者要對使用中的保存時間和情況負責，一般是在2°C–8°C下不能超過24小時。

包裝

每一個小瓶中含20毫升供輸注用溶液。

單瓶盒裝。

資料日期

2009年6月

許可證持有者/包裝廠：Merck KGaA
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製造廠：Boehringer Ingelheim Pharma GmbH & Co KG
廠 址：Birkendorfer Strasse 65, 88397 Biberach , Germany

藥 商：台灣默克股份有限公司
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ERBITUX[®]**(Cetuximab)**

For intravenous use only.

WARNING

Infusion Reactions: Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension (see **WARNINGS** and **ADVERSE REACTIONS**). Severe infusion reactions require immediate interruption of the ERBITUX infusion and permanent discontinuation from further treatment. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

DESCRIPTION

ERBITUX[®] (Cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). ERBITUX is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. ERBITUX is produced in mammalian (murine myeloma) cell culture.

ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

28 CLINICAL PHARMACOLOGY

29 General

30 ERBITUX binds specifically to the epidermal growth factor receptor (EGFR, HER1,
31 c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of
32 epidermal growth factor (EGF) and other ligands, such as transforming growth factor-
33 alpha. Binding of ERBITUX to the EGFR blocks phosphorylation and activation of
34 receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis,
35 and decreased matrix metalloproteinase and vascular endothelial growth factor
36 production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily
37 of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4.
38 The EGFR is constitutively expressed in many normal epithelial tissues, including the
39 skin and hair follicle. Over-expression of EGFR is also detected in many human cancers
40 including those of the colon and rectum.

41 *In vitro* assays and *in vivo* animal studies have shown that ERBITUX inhibits the growth
42 and survival of tumor cells that over-express the EGFR. No anti-tumor effects of
43 ERBITUX were observed in human tumor xenografts lacking EGFR expression. The
44 addition of ERBITUX to irinotecan or irinotecan plus 5-fluorouracil in animal studies
45 resulted in an increase in anti-tumor effects compared to chemotherapy alone.

46 Human Pharmacokinetics

47 ERBITUX administered as monotherapy or in combination with concomitant
48 chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the
49 concentration time curve (AUC) increased in a greater than dose proportional manner as
50 the dose increased from 20 to 400 mg/m². ERBITUX clearance (CL) decreased from 0.08
51 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m², and at doses >200 mg/m², it
52 appeared to plateau. The volume of the distribution (Vd) for ERBITUX appeared to be
53 independent of dose and approximated the vascular space of 2-3 L/m².

54 Following a 2-hour infusion of 400 mg/m² of ERBITUX, the maximum mean serum
55 concentration (C_{max}) was 184 µg/mL (range: 92-327 µg/mL) and the mean elimination
56 half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m² produced a
57 mean C_{max} of 140 µg/mL (range 120-170 µg/mL). Following the recommended dose
58 regimen (400 mg/m² initial dose/250 mg/m² weekly dose), ERBITUX concentrations

59 reached steady-state levels by the third weekly infusion with mean peak and trough
60 concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively.
61 The mean half-life was 114 hours (range 75-188 hours).

62 **Special Populations**

63 A population pharmacokinetic analysis was performed to explore the potential effects of
64 selected covariates including race, gender, age, and hepatic and renal function on
65 ERBITUX pharmacokinetics.

66 Female patients had a 25% lower intrinsic ERBITUX clearance than male patients. The
67 toxicity profile was similar in males and females. Definitive conclusions regarding
68 comparability in efficacy cannot be made given the small number of patients with
69 objective tumor responses. None of the other covariates explored appeared to have an
70 impact on ERBITUX pharmacokinetics.

71 ERBITUX has not been studied in pediatric populations.

72 **CLINICAL STUDIES**

73 The efficacy and safety of ERBITUX alone or in combination with irinotecan were
74 studied in a randomized, controlled trial (329 patients) and in combination with
75 irinotecan in an open-label, single-arm trial (138 patients). ERBITUX was further
76 evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111
77 patients treated with single-agent ERBITUX was also evaluated. All trials studied
78 patients with EGFR-expressing, metastatic colorectal cancer, whose disease had
79 progressed after receiving an irinotecan-containing regimen.

80 **Randomized, Controlled Trial**

81 A multicenter, randomized, controlled clinical trial was conducted in 329 patients
82 randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX
83 monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a
84 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or
85 unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the
86 ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose
87 and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan
88 schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m²
89 weekly times four doses every 6 weeks. An Independent Radiographic Review

Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ≥ 80 . Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment.

The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in all randomized patients.

Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with ERBITUX, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen.

The objective response rates (ORR) in these populations are presented in Table 1.

Table 1: Objective Response Rates per Independent Review

Populations	ERBITUX + Irinotecan		ERBITUX Monotherapy		Difference (95% CI ^a)	
	n	ORR (%)	n	ORR (%)	%	p-value CMH ^b
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
• Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8 - 25.6)	0.09
• Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

^a95% confidence interval for the difference in objective response rates.

^bCochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients

114 randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan
 115 experienced a significantly longer median time to disease progression (see Table 2).

Table 2: Time to Progression per Independent Review

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI ^a)	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 – 0.71)	<0.001
• Irinotecan- Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
• Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

116 ^aHazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.
 117

118 Single-Arm Trials

119 ERBITUX, in combination with irinotecan, was studied in a single-arm, multicenter,
 120 open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal
 121 cancer who had progressed following an irinotecan-containing regimen. Patients received
 122 a 20-mg test dose of ERBITUX on day 1, followed by a 400-mg/m² initial dose, and
 123 250 mg/m² weekly until disease progression or unacceptable toxicity. Patients received
 124 the same dose and schedule for irinotecan as the patient had previously failed. Acceptable
 125 irinotecan schedules were 350 mg/m² every 3 weeks or 125 mg/m² weekly times four
 126 doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression
 127 to irinotecan as determined by an IRC. The overall response rate was 15% for the overall
 128 population and 12% for the irinotecan-failure population. The median durations of
 129 response were 6.5 and 6.7 months, respectively.

130 ERBITUX was studied as a single agent in a multicenter, open-label, single-arm clinical
 131 trial in patients with EGFR-expressing, metastatic colorectal cancer who progressed
 132 following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had
 133 documented progression to irinotecan. The overall response rate was 9% for the all-
 134 treated group and 14% for the irinotecan-failure group. The median times to progression
 135 were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months
 136 for both groups.

EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDxTM test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

INDICATIONS AND USAGE

ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

ERBITUX administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

The effectiveness of ERBITUX is based on objective response rates (see **CLINICAL STUDIES**). Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX.

CONTRAINDICATIONS

None.

WARNINGS

Infusion Reactions (See **BOXED WARNING: Infusion Reactions, ADVERSE REACTIONS: Infusion Reactions, and DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% (20/774) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion

167 reaction during later infusions. A 1-hour observation period is recommended following
168 the ERBITUX infusion. Longer observation periods may be required in patients who
169 experience infusion reactions.

170 Severe infusion reactions require the immediate interruption of ERBITUX therapy and
171 permanent discontinuation from further treatment. Appropriate medical therapy including
172 epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen
173 should be available for use in the treatment of such reactions. Patients should be carefully
174 observed until the complete resolution of all signs and symptoms.

175 In clinical trials, mild to moderate infusion reactions were managed by slowing the
176 infusion rate of ERBITUX and by continued use of antihistamine medications (eg,
177 diphenhydramine) in subsequent doses (see **DOSAGE AND ADMINISTRATION:**
178 **Dose Modifications**).

179 **Pulmonary Toxicity**

180 Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced
181 colorectal cancer receiving ERBITUX. Interstitial pneumonitis with non-cardiogenic
182 pulmonary edema resulting in death was reported in one case. Two patients had pre-
183 existing fibrotic lung disease and experienced an acute exacerbation of their disease while
184 receiving ERBITUX in combination with irinotecan. In the clinical investigational
185 program, an additional case of interstitial pneumonitis was reported in a patient with head
186 and neck cancer treated with ERBITUX and cisplatin. The onset of symptoms occurred
187 between the fourth and eleventh doses of treatment in all reported cases.

188 In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should
189 be interrupted and a prompt investigation of these symptoms should occur. If ILD is
190 confirmed, ERBITUX should be discontinued and the patient should be treated
191 appropriately.

192 **Dermatologic Toxicity (See **ADVERSE REACTIONS:****

193 **Dermatologic Toxicity and **DOSAGE AND ADMINISTRATION:****

194 **Dose Modifications**.)

195 In cynomolgus monkeys, ERBITUX, when administered at doses of approximately 0.4 to
196 4 times the weekly human exposure (based on total body surface area), resulted in
197 dermatologic findings, including inflammation at the injection site and desquamation of
198 the external integument. At the highest dose level, the epithelial mucosa of the nasal

199 passage, esophagus, and tongue were similarly affected, and degenerative changes in the
200 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of
201 the animals at the highest dose level beginning after approximately 13 weeks of
202 treatment.

203 In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin
204 drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis,
205 cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash
206 was reported in 89% (686/774) of all treated patients, and was severe (Grade 3 or 4) in
207 11% (84/774) of these patients. Subsequent to the development of severe dermatologic
208 toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and
209 drainage were reported.

210 Patients developing dermatologic toxicities while receiving ERBITUX should be
211 monitored for the development of inflammatory or infectious sequelae, and appropriate
212 treatment of these symptoms initiated. Dose modifications of any future ERBITUX
213 infusions should be instituted in case of severe acneform rash (see **DOSAGE AND**
214 **ADMINISTRATION, Table 4**). Treatment with topical and/or oral antibiotics should be
215 considered; topical corticosteroids are not recommended.

216 **PRECAUTIONS**

217 **General**

218 ERBITUX therapy should be used with caution in patients with known hypersensitivity
219 to Cetuximab, murine proteins, or any component of this product.

220 It is recommended that patients wear sunscreen and hats and limit sun exposure while
221 receiving ERBITUX as sunlight can exacerbate any skin reactions that may occur.

222 **EGF Receptor Testing**

223 Patients enrolled in the clinical studies were required to have immunohistochemical
224 evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test
225 kit. Assessment for EGFR expression should be performed by laboratories with
226 demonstrated proficiency in the specific technology being utilized. Improper assay
227 performance, including use of suboptimally fixed tissue, failure to utilize specified
228 reagents, deviation from specific assay instructions, and failure to include appropriate
229 controls for assay validation, can lead to unreliable results. Refer to the DakoCytomation

230 test kit package insert for full instructions on assay performance. (See **CLINICAL**
231 **STUDIES: EGFR Expression and Response.**)

232 **Laboratory Tests: Electrolyte Monitoring**

233 Patients should be periodically monitored for hypomagnesemia, and accompanying
234 hypocalcemia and hypokalemia, during and following the completion of ERBITUX
235 therapy. Monitoring should continue for a period of time commensurate with the half-life
236 and persistence of the product; i.e., 8 weeks. (See **ADVERSE REACTIONS:**
237 **Electrolyte Depletion.**)

238 **Drug Interactions**

239 A drug interaction study was performed in which ERBITUX was administered in
240 combination with irinotecan. There was no evidence of any pharmacokinetic interactions
241 between ERBITUX and irinotecan.

242 **Immunogenicity**

243 As with all therapeutic proteins, there is potential for immunogenicity. Potential
244 immunogenic responses to ERBITUX were assessed using either a double antigen
245 radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay
246 performance and sampling timing, the incidence of antibody development in patients
247 receiving ERBITUX has not been adequately determined. The incidence of antibodies to
248 ERBITUX was measured by collecting and analyzing serum pre-study, prior to selected
249 infusions and during treatment follow-up. Patients were considered evaluable if they had
250 a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-
251 ERBITUX antibodies were detected in 5% (28 of 530) of evaluable patients. In patients
252 positive for anti-ERBITUX antibody, the median time to onset was 44 days (range 8-281
253 days). Although the number of sero-positive patients is limited, there does not appear to
254 be any relationship between the appearance of antibodies to ERBITUX and the safety or
255 antitumor activity of the molecule.

256 The observed incidence of anti-ERBITUX antibody responses may be influenced by the
257 low sensitivity of available assays, inadequate to reliably detect lower antibody titers.
258 Other factors which might influence the incidence of anti-ERBITUX antibody response
259 include sample handling, timing of sample collection, concomitant medications, and

260 underlying disease. For these reasons, comparison of the incidence of antibodies to
261 ERBITUX with the incidence of antibodies to other products may be misleading.

262 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

263 Long-term animal studies have not been performed to test ERBITUX for carcinogenic
264 potential. No mutagenic or clastogenic potential of ERBITUX was observed in the
265 *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-
266 week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of
267 ERBITUX (based on total body surface area) revealed a tendency for impairment of
268 menstrual cycling in treated female monkeys, including increased incidences of
269 irregularity or absence of cycles, when compared to control animals, and beginning from
270 week 25 of treatment and continuing through the 6-week recovery period. Serum
271 testosterone levels and analysis of sperm counts, viability, and motility were not
272 remarkably different between ERBITUX-treated and control male monkeys. It is not
273 known if ERBITUX can impair fertility in humans.

274 **Pregnancy Category C**

275 Animal reproduction studies have not been conducted with ERBITUX. However, the
276 EGFR has been implicated in the control of prenatal development and may be essential
277 for normal organogenesis, proliferation, and differentiation in the developing embryo. In
278 addition, human IgG1 is known to cross the placental barrier; therefore ERBITUX has
279 the potential to be transmitted from the mother to the developing fetus. It is not known
280 whether ERBITUX can cause fetal harm when administered to a pregnant woman or
281 whether ERBITUX can affect reproductive capacity. There are no adequate and well-
282 controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to
283 a pregnant woman, or any woman not employing adequate contraception if the potential
284 benefit justifies the potential risk to the fetus. All patients should be counseled regarding
285 the potential risk of ERBITUX treatment to the developing fetus prior to initiation of
286 therapy. If the patient becomes pregnant while receiving this drug, she should be
287 apprised of the potential hazard to the fetus and/or the potential risk for loss of the
288 pregnancy.

289 **Nursing Mothers**

290 It is not known whether ERBITUX is secreted in human milk. Because human IgG is
291 secreted in human milk, the potential for absorption and harm to the infant after ingestion

exists. Based on the mean half-life of ERBITUX after multiple dosing of 114 hours [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human Pharmacokinetics**), women should be advised to discontinue nursing during treatment with ERBITUX and for 60 days following the last dose of ERBITUX.

Pediatric Use

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

Geriatric Use

Of the 774 patients who received ERBITUX with irinotecan or ERBITUX monotherapy in four advanced colorectal cancer studies, 253 patients (33%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

ADVERSE REACTIONS

Except where indicated, the data described below reflect exposure to ERBITUX in 774 patients with advanced metastatic colorectal cancer. ERBITUX was studied in combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving ERBITUX plus irinotecan received a median of 12 doses [with 88/354 (25%) treated for over 6 months], and patients receiving ERBITUX monotherapy received a median of 7 doses [with 36/420 (9%) treated for over 6 months]. The population had a median age of 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving ERBITUX monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with ERBITUX were:

- Infusion reaction (3%) (see **BOXED WARNING, WARNINGS, and DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Dermatologic toxicity (1%) (see **WARNINGS and DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Interstitial lung disease (0.4%) (see **WARNINGS**);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);

322 • Pulmonary embolus (1%);
323 • Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients
324 receiving ERBITUX monotherapy;
325 • Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0.2% in patients
326 receiving ERBITUX monotherapy.

327 Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 17 (4%) patients
328 receiving ERBITUX monotherapy discontinued treatment primarily because of adverse
329 events.

330 The most common adverse events seen in 354 patients receiving ERBITUX plus
331 irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea
332 (55%), abdominal pain (45%), and vomiting (41%).

333 The most common adverse events seen in 420 patients receiving ERBITUX monotherapy
334 were acneform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%),
335 constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%).

336 Because clinical trials are conducted under widely varying conditions, adverse reaction
337 rates observed in the clinical trials of a drug cannot be directly compared to rates in the
338 clinical trials of another drug and may not reflect the rates observed in practice. The
339 adverse reaction information from clinical trials does, however, provide a basis for
340 identifying the adverse events that appear to be related to drug use and for approximating
341 rates.

342 Data in patients with advanced colorectal carcinoma in Table 3 are based on the
343 experience of 354 patients treated with ERBITUX plus irinotecan and 420 patients
344 treated with ERBITUX monotherapy.

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term ¹	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise ²	73	16	48	10
Abdominal Pain	45	8	26	9
Fever ³	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction ⁴	19	3	21	2
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
Digestive				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea ³	23	2	17	7
Cough Increased	20	0	11	1

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term ¹	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Skin/Appendages				
Acneform Rash ⁵	88	14	90	8
Alopecia	21	0	4	0
Skin Disorder	15	1	4	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	11	<1
Conjunctivitis	14	1	7	<1

¹ Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.

² Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.

³ Includes cases reported as infusion reaction.

⁴ Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever”, or “dyspnea”.

⁵ Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

345 **Infusion Reactions (see **BOXED WARNING: Infusion Reactions**)**

346 In clinical trials, severe, potentially fatal infusion reactions were reported. These events
 347 include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness),
 348 urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion
 349 reactions were observed in 3% of patients receiving ERBITUX plus irinotecan and 2% of
 350 patients receiving ERBITUX monotherapy. Grade 1 and 2 infusion reactions, including
 351 chills, fever, and dyspnea usually occurring on the first day of initial dosing, were
 352 observed in 16% of patients receiving ERBITUX plus irinotecan and 19% of patients
 353 receiving ERBITUX monotherapy. (See **WARNINGS: Infusion Reactions** and
 354 **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

355 In the clinical studies described above, a 20-mg test dose was administered intravenously
356 over 10 minutes prior to the loading dose to all patients. The test dose did not reliably
357 identify patients at risk for severe allergic reactions.

358 **Dermatologic Toxicity and Related Disorders**

359 Non-suppurative acneform rash described as “acne”, “rash”, “maculopapular rash”,
360 “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving
361 ERBITUX plus irinotecan or ERBITUX monotherapy. One or more of the
362 dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving
363 ERBITUX plus irinotecan and in 90% (8% Grade 3) of patients receiving ERBITUX
364 monotherapy. Acneform rash most commonly occurred on the face, upper chest, and
365 back, but could extend to the extremities and was characterized by multiple follicular- or
366 pustular-appearing lesions. Skin drying and fissuring were common in some instances,
367 and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis,
368 cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was
369 generally within the first two weeks of therapy. Although in a majority of the patients the
370 event resolved following cessation of treatment, in nearly half of the cases, the event
371 continued beyond 28 days. (See **WARNINGS: Dermatologic Toxicity** and **DOSAGE**
372 **AND ADMINISTRATION: Dose Modifications**.)

373 A related nail disorder, occurring in 14% of patients (0.4% Grade 3), was characterized
374 as a paronychia inflammation with associated swelling of the lateral nail folds of the toes
375 and fingers, with the great toes and thumbs as the most commonly affected digits.

376 **Use with Radiation Therapy**

377 In a study of 21 patients with locally advanced squamous cell cancer of the head and
378 neck, patients treated with ERBITUX, cisplatin, and radiation had a 95% incidence of
379 rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined
380 modality therapy appears to be additive, particularly within the radiation port. The
381 addition of radiation to ERBITUX therapy in patients with colorectal cancer should be
382 done with appropriate caution.

383 **Electrolyte Depletion**

384 In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of
385 hypomagnesemia, both overall and severe (NCI-CTC Grades 3 and 4), was increased in

386 patients receiving ERBITUX alone or in combination with chemotherapy as compared to
387 those receiving best supportive care or chemotherapy alone. Approximately one-half of
388 these patients receiving ERBITUX experienced hypomagnesemia and 10-15%
389 experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been
390 reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion
391 was necessary in some patients and in severe cases, intravenous replacement was
392 required. The time to resolution of electrolyte abnormalities is not well known, hence
393 monitoring after ERBITUX treatment is recommended. (See **PRECAUTIONS:**
394 **Laboratory Tests.**)

395 **OVERDOSAGE**

396 Single doses of ERBITUX higher than 500 mg/m² have not been tested. There is no
397 experience with overdosage in human clinical trials.

398 **DOSAGE AND ADMINISTRATION**

399 The recommended dose of ERBITUX, in combination with irinotecan or as monotherapy,
400 is 400 mg/m² as an initial loading dose (first infusion) administered as a 120-minute IV
401 infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance
402 dose (all other infusions) is 250 mg/m² infused over 60 minutes (maximum infusion rate
403 5 mL/min). Premedication with an H₁ antagonist (eg, 50 mg of diphenhydramine IV) is
404 recommended. Appropriate medical resources for the treatment of severe infusion
405 reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion**
406 **Reactions.**)

407 **Dose Modifications**

408 **Infusion Reactions**

409 If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the
410 infusion rate should be permanently reduced by 50%.

411 ERBITUX should be immediately and permanently discontinued in patients who
412 experience severe (Grade 3 or 4) infusion reactions. (See **WARNINGS** and **ADVERSE**
413 **REACTIONS.**)

414 **Dermatologic Toxicity and Related Disorders**

415 If a patient experiences severe acneform rash, ERBITUX treatment adjustments should
416 be made according to Table 4. In patients with mild and moderate skin toxicity, treatment
417 should continue without dose modification. (See **WARNINGS** and **ADVERSE**
418 **REACTIONS**.)

Table 4: ERBITUX Dose Modification Guidelines

Severe Acneform Rash	ERBITUX	Outcome	ERBITUX Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m ²
		No Improvement	Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m ²
		No Improvement	Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m ²
		No Improvement	Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

419 **Preparation for Administration**

420 DO NOT ADMINISTER ERBITUX AS AN IV PUSH OR BOLUS.

421 **ERBITUX must be administered with the use of a low protein binding 0.22-**
422 **micrometer in-line filter.**

423 ERBITUX is supplied as a 50-mL, single-use vial containing 100 mg of Cetuximab at a
424 concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and
425 colorless and may contain a small amount of easily visible, white, amorphous, Cetuximab
426 particulates. **DO NOT SHAKE OR DILUTE.**

427 USING APPROPRIATE ASEPTIC TECHNIQUE, ERBITUX SHOULD BE
428 ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

429 **Infusion Pump:**

- 430 • Draw up the volume of a vial using a sterile syringe attached to an appropriate
431 needle (a vented spike or other appropriate transfer device may be used).

- 432 • Fill ERBITUX into a sterile evacuated container or bag such as glass containers,
433 polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter
434 Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- 435 • Repeat procedure until the calculated volume has been put into the container. Use
436 a new needle for each vial.
- 437 • Administer through a low protein binding 0.22-micrometer in-line filter (placed as
438 proximal to the patient as practical).
- 439 • Affix the infusion line and prime it with ERBITUX before starting the infusion.
- 440 • Maximum infusion rate should not exceed 5 mL/min.
- 441 • Use 0.9% saline solution to flush line at the end of infusion.

442 **Syringe Pump:**

- 443 • Draw up the volume of a vial using a sterile syringe attached to an appropriate
444 needle (a vented spike may be used).
- 445 • Place the syringe into the syringe driver of a syringe pump and set the rate.
- 446 • Administer through a low protein binding 0.22-micrometer in-line filter rated for
447 syringe pump use (placed as proximal to the patient as practical).
- 448 • Connect up the infusion line and start the infusion after priming the line with
449 ERBITUX.
- 450 • Repeat procedure until the calculated volume has been infused.
- 451 • Use a new needle and filter for each vial.
- 452 • Maximum infusion rate should not exceed 5 mL/min.
- 453 • Use 0.9% saline solution to flush line at the end of infusion.

454 **ERBITUX should be piggybacked to the patient's infusion line.**

455 **Following the ERBITUX infusion, a 1-hour observation period is recommended.**
456 **Longer observation periods may be required in those who experience infusion**
457 **reactions.**

458 **HOW SUPPLIED**

459 ERBITUX[®] (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of
460 Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one
461 ERBITUX vial (NDC 66733-948-23).

Stability and Storage

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of ERBITUX in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

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ERBITUX[®] is a registered trademark of ImClone Systems Incorporated.

Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876

Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543



**ImClone Systems
Incorporated**



Bristol-Myers Squibb Company

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