MERCK

台灣默克股份有限公司 函

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受文者：裕利股份有限公司/吉程股份有限公司/裕翔藥品股份有限公司

副本：中華民國藥師公會全聯會/社團法人台灣臨床藥學會/台灣年輕藥師學會

發文日期：中華民國一百零六年六月十二日
發文字號：台灣默克藥字第106060 號
密等及解密條件：普通

主旨：「Erbitux 5mg/ml Solution for Infusion爾必得舒注射液5毫克/毫升」，新增原料藥及成品製造廠及架儲期變更事宜，如說明。

一、 本公司產品「Erbitux 5mg/ml Solution for Infusion 爾必得舒注射液 5 毫克/毫升」申請(I.)新增原料藥及成品製造廠 (II.)架儲期變更，已獲衛福部核准。自一百零六年七月中旬出貨產品的仿單、標籤及外盒，將開始標示此變更。

I. 新增原料藥及成品製造廠:Boehringer Ingelheim Pharma GmbH & Co. KG (Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany), 為備用供應製造來源, 俾利藥品調度;目前 Erbitux 產品全數維持由本公司德國原廠 Merck KGaA 生產製造, 供貨穩定流暢

II. 架儲期由 36 個月變更為 48 個月

二、 除上述外，其餘成份、含量、療效、健保代碼、健保核價均維持不變。

此致

台灣默克股份有限公司
代表負責人　謝　志　宏

附件：藥品許可證、衛福部許可函、中文仿單核定本、外盒包裝及藥瓶貼標核定本

台灣默克股份有限公司
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行政院衛生署細菌學免疫學製品許可證

衛署菌疫輸 字第 000877 號

簽審文件號碼：DHA01000087701

中文名稱： 爾必得舒® 注射液 5 毫克/毫升

英文名稱： Erbitux® 5mg/ml Solution for infusion

類　　別： 本藥限由醫師使用

藥商名稱： 台灣默克股份有限公司

劑　　型： 注射劑

製造廠名稱： BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

包裝種類： 20 毫升小瓶裝，100 支以下盒裝。

製造廠地址： BIRKENDORFER STRASSE 65, 88397 BIBERACH, GERMANY 續如後

處　　方：

Each ml contains：

Cetuximab, Chimeric Antibody……5.00 mg

適 應 症： 詳如後

前項藥品經本署審核與藥事法之規定相符應發給許可證以資證明

行政院衛生署署長

葉金川

發證日期　玖拾捌　年　參　月　拾壹　日

有效日期　壹佰零參　年　參　月　拾壹　日

核准展延至	108年 3 月 11 日	年　月　日	年　月　日	年　月　日
文號	036000793			

H 000814

變更事項	核准文號	核准日期	變更事項	核准文號	核准日期
其					
適應症變更 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的病患。 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。	0980345435	98.11.27	**製造廠地址變更(門牌整編)** BIRKENDORFER STRASSE 65, 88397 BIBERACH AN DER RISS, GERMANY	1036013373	103.3.21
他			**適應症變更** Erbitux 適用於治療具表皮生長因子受體表現型 (EGFR expressing)，RAS 原生型 (wild-type)之轉移性直腸結腸癌患者 • 與 FOLFIRI (Folinic acid/ 5-FU/ Irinotecan) 合併使用之第一線治療。 • 與 FOLFOX 合併使用之第一線治療。 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。	1036041536	103.4.22
他	1001400111	100.1.5	新增原料藥及成品製造廠： Boehringer Ingelheim Pharma GmbH&Co. KG (Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany)。	1015006421	103.2.16
他			**刊載原料藥製造廠：** 廠名：BOEHRINGER INGELHEIM Pharma GmbH & Co., KG 廠址：BIRKENDORFER STRASSE 65, 88397 BIBERACH AN DER RISS, GERMANY		104.5.23

申請變更項目：變更產地，變更為：

(一)主製造廠：MERCK KGaA (廠址：FRANKFURTER STRASSE 250, D-64293 DARMSTADT, GERMANY)，負責製程：自濃縮原料藥(Concentrated bulk)之稀釋(Dilution 或 Formulation)作業至成品製劑、一級及二級包裝作業。

(二)次製造廠：MERCK SERONO S.A.-CORSIER-SUR-VEVEY(廠址：ROUTE DE FENIL, 25 ZONE INDUSTRIELLE B, 1804 CORSIER-SUR-VEVEY, SWITZERLAND)，負責製程：原料藥(Cetuximab)自工作細胞庫至濃縮原料藥(Concentrated bulk)之製造階段。

104.12.16

1041412585

LICENSE HOLDER/PACKING : MERCK KGaA (FRANKFURTER STRASSE 250, D-64293 DARMSTADT, GERMANY)

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的病患。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。

檔　　號：
保存年限：

正本

衛生福利部　函

機關地址：11558 台北市南港區忠孝東路六段488號
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受文者：台灣默克股份有限公司

正本
FEB 20 2017

發文日期：中華民國106年2月17日
發文字號：衛授食字第1051590011號
速別：
密等及解密條件或保密期限：
附件：藥品許可證及標仿單核定本各一份

主旨：貴公司申請許可證衛署菌疫輸字第000877號「爾必得舒注射液 5 毫克/毫升」變更登記一案(案號：1051590011)，准予備查，隨函檢還藥品許可證及標仿單核定本各一份，復請查照。

說明：

一、復貴公司105年9月30日台灣默克藥字第105098號藥品變更登記申請書。

二、申請變更項目：

(一)新增原料藥及成品製造廠：Boehringer Ingelheim Pharma GmbH&Co. KG(Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany)。

(二)架儲期變更為48個月。

(三)仿單、標籤及外盒變更。

正本：台灣默克股份有限公司
副本：

部長陳時中

仿單標籤粘貼表

產品名稱	爾必得舒注射液 5 毫克／毫升	申請廠商	台灣默克股份有限公司
衛生福利部 食品藥物管理署給證號碼	衛署菌疫輸字第 000877 號		

106.02.14

直腸結腸癌併有 RAS 突變型腫瘤

Erbitux®不可用來治療具腫瘤有 RAS 突變型或 RAS 腫瘤狀況未知的直腸結腸癌患者，在臨床研究顯示對於 RAS 突變型的腫瘤沒有療效。在臨床研究特別指出 cetuximab 併用 FOLFOX4 對這些患者的無惡化存活期(PFS)和存活期(OS)有負面影響(見"特性")。

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

氣管痙攣和藥疹。儘管事先給藥預防，仍可能會發生。
有對紅肉或高蝨叮咬過敏之病史，或對抗 cetuximab 的 IgE 抗體（α-1-3-半乳糖）試驗結果呈陽性的患者，發生過敏反應的風險大大提高。在這些患者，需經過仔細評估過效益/風險(包括替代療法)，並且只有在訓練有素的人員嚴密監督，且備妥急救設備的情況下，方可給予 cetuximab。
首次劑量應緩慢給藥，速率不得超過 5 毫克/分鐘 (mg/min)，同時嚴密監控所有的生命徵象至少兩小時。如果在第一次輸注時，輸注相關反應在頭 15 分鐘內發生，應停止輸注。應該仔細評估效益/風險，包括考慮患者是否可能已存在 IgE 抗體後，才能給予後續輸注。
如果輸注相關反應在稍後的輸注過程中或後續輸注時發生，進一步的處理將取決於其嚴重程度：
a）第 1 級：在嚴密監督下繼續緩慢輸注

與 fluoropyrimidines 合併使用時，心臟局部缺血的症狀包括心肌梗塞、充血性心衰竭及手足症候群（手足皮膚紅斑、感覺異常）的發生頻率較 fluoropyrimidines 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特性都沒有改變。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。

用法用量

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輸注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。
首次劑量應緩慢給藥，輸注速率不可超過 5 毫克/分。

直腸結腸癌

Erbitux®與化學治療合併使用於治療轉移性之直腸結腸癌患者(見"特性")。
開始用 Erbitux®的治療之前，必須確定是 RAS（KRAS 和 NRAS）原生型。突變狀態應該由有經驗的實驗室使用確效之方法檢測 KRAS exon 2,3,4 和 NRAS exon 2,3,4 的突變來確定（見"特性"和"特別警告和注意事項"）。
併用化學治療藥物的劑量或建議調整劑量，參閱其相關之個別產品資訊。必須在輸注 cetuximab 一小時之後，才能給予後續之化學療法。
建議持續 cetuximab 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。

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"部分所提到的之外），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℃ - 8℃）。
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/毫升若依上述方法配製，使用中的化學和物理安定性在 25℃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℃ - 8℃ 下不能超過 24 小時。

包裝

每一個藥瓶中有 20 毫升供輸注用溶液。
單瓶盒裝。

資料日期

2017 年 3 月

主製造廠 1
Merck KGaA
Frankfurter Strasse 250, D-64293 Darmstadt, Germany

主製造廠 2
Boehringer Ingelheim Pharma GmbH & Co.KG
Birkendorfer Strasse 65, 88397 Biberach An Der Riss, Germany

包裝廠
Merck KGaA
Frankfurter Strasse 250, D-64293 Darmstadt, Germany

藥 商：台灣默克股份有限公司
地 址：台北市內湖區堤頂大道二段 89 號 6 樓
電 話：(02) 2162-1111

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　衛署菌疫輸字第 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）、甘胺酸（glycine）、聚乙二醇山梨酯 80（polysorbate 80）、單水檸檬酸（citric acid monohydrate）、氫氧化鈉（sodium hydroxide）、和注射用水(water for injection)。

特性
作用機轉
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 IgG_1 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 不與其它 HER 的受體結合。
原致癌基因（proto-oncogene）RAS（rat sarcoma）的蛋白質產物，為表皮生長因子受體（EGFR）一個重要的下游訊號傳遞者；在腫瘤中，經由表皮生長因子受體活化的 RAS，可進一步促成表皮生長因子受體媒介(EGFR-mediated）增加增殖、存活及產生血管生成前驅因子（pro-angiogenic factor）。
RAS 是人類癌症中最常被活化的致癌基因（oncogene）家族之一，在外顯子(exon) 2、3、4 上某些突變好發點(hot spot)突變的 RAS 基因會導致其表皮生長因子受體訊號傳遞過程中之 RAS 蛋白不受控制的持續活化。

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
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。對直腸結腸癌轉移的患者的臨床試驗篩檢中，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。腫瘤未偵測到 EGFR 的患者使用 cetuximab 的療效與安全性尚未確立。
在試驗報告中顯示，cetuximab 治療或 cetuximab 合併化學治療用在有 RAS 突變之轉移性直腸結腸癌患者很難有臨床效益；而當 cetuximab 搭配 FOLFOX4 治療時，在 RAS 突變族群的疾病無惡化存活期(PFS)有顯著的負面影響。
針對 EMR 62 202-013 和 EMR 62 202-047 試驗，還進行了除了 KRAS 基因第 2 外顯子以外的其他 RAS 基因突變（NRAS 和 KRAS）的事後分析(post hoc analysis)，臨床試驗 EMR 62 202-007 無法執行事後分析。

Cetuximab 合併化學療法治療：
- EMR 62 202-013：此隨機分配臨床試驗，針對先前未接受治療之轉移性直腸結腸癌患者，投予 cetuximab 與 irinotecan 及 5-fluorouracil/folinic acid（FOLFIRI）合併治療（599 位患者），與僅接受相同之化學療法（599 位患者）相比較。在可評估 KRAS 狀態的患者中，其腫瘤表現為 KRAS 原生型（wild-type）之患者比例為 63%。為了評估 RAS 基因突變狀態，對其 KRAS 第二外顯子原生型之患者所有可獲得的腫瘤樣本都進行了除 KRAS 基因第 2 外顯子突變以外的其他突變狀態檢測。因此，具 RAS 突變型之患者族群包括 KRAS 基因第 2 外顯子以及其他 RAS 基因呈現突變狀態的患者。

其治療結果摘要如下：:

變數/統計	具 RAS 原生型之受試者		具 RAS 突變型之受試者	
	Cetuximab 合併 FOLFIRI（N=178）	FOLFIRI（N=189）	Cetuximab 合併 FOLFIRI（N=246）	FOLFIRI（N=214）
存活期				
月，中數 (95% CI)	28.4 (24.7, 31.6)	20.2 (17.0, 24.5)	16.4 (14.9, 18.4)	17.7 (15.4, 19.6)
Hazard 比(95%CI)	0.691 (0.543, 0.879)		1.049 (0.860, 1.281)	
p-值	0.0024		0.6355	
疾病無惡化存活期				
月，中數 (95% CI)	11.4 (10.0, 14.6)	8.4 (7.4, 9.4)	7.4 (6.4, 8.0)	7.5 (7.2, 8.5)
Hazard 比(95%CI)	0.556 (0.406, 0.761)		1.098 (0.852, 1.415)	
p-值	0.0002		0.4696	
客觀反應率				
百分比 (95% CI)	66.3 (58.8, 73.2)	38.6 (31.7, 46.0)	31.7 (25.9, 37.9)	36.0 (29.6, 42.8)
勝算比(95% CI)	3.1145 (2.0279, 4.7835)		0.8478 (0.5767, 1.2462)	
p-值	< 0.0001		0.3970	

CI=confidence interval 信賴區間, FOLFIRI = irinotecan + 5 fluorouracil/folinic acid, ORR=objective response rate 客觀反應率（完全反應及部分反應之患者），OS=overall survival time 存活期, PFS=progression-free survival time 疾病無惡化存活期。有檢測 KRAS 者占所有受試者的 88.7% (1063/1198)。

對所有患者而言，cetuximab 合併 irinotecan+5-fluorouracil/folinic acid (FOLFIRI)靜脈輸注，其存活期（19.9 月 vs. 18.6 月; p=0.0420; HR 0.878）、疾病無惡化存活期(8.9 月 vs. 8.0 月; p=0.0479; HR 0.851)及客觀反應率(46.9% vs. 38.7 %; p=0.0038)都有顯著的改善。

- EMR 62 202-047：此隨機分配臨床試驗，針對先前未接受治療之轉移性直腸結腸癌患者，投予 cetuximab 與 oxaliplatin 加連續輸注 5-fluorouracil/folinic acid（FOLFOX4）合併治療（169 位患者），與僅接受相同之化學療法（168 位患者）相比較。在可評估 KRAS 狀態的患者中，其腫瘤表現為 KRAS 原生型之患者比例為 57%。為了評估整體 RAS 突變狀態，對其 KRAS 第 2 外顯子原生型之患者所有可獲得的腫瘤樣本都進行了除 KRAS 基因第 2 外顯子突變以外的其他 RAS 突變之突變狀態分析。具 RAS 突變型之患者族群包括 KRAS 基因第 2 外顯子以及其他 RAS 基因呈現突變狀態的患者。

其治療結果摘要如下：

變數/統計	具 RAS 原生型之受試者		具 RAS 突變型之受試者	
	Cetuximab 合併 FOLFOX4（N=38）	FOLFOX4（N=49）	Cetuximab 合併 FOLFOX4（N=92）	FOLFOX4（N=75）
存活期				
月，中數 (95% CI)	19.8 (16.6, 25.4)	17.8 (13.8, 23.9)	13.5 (12.1, 17.7)	17.8 (15.9, 23.6)
Hazard 比(95%CI)	0.937 (0.563, 1.558)		1.291 (0.905, 1.842)	
p-值	0.8002		0.1573	
疾病無惡化存活期				
月，中數 (95% CI)	12.0 (5.8, NE)	5.8 (4.7 7.9)	5.6 (4.4, 7.5)	7.8 (6.7, 9.3)
Hazard 比(95%CI)	0.533 (0.272, 1.042)		1.541 (1.037, 2.289)	
p-值	0.0615		0.0309	
客觀反應率				
百分比 (95% CI)	57.9 (40.8, 73.7)	28.6 (16.6, 43.3)	37.0 (27.1, 47.7)	50.7 (38.9, 62.4)
勝算比(95% CI)	3.3302 (1.375, 8.172)		0.580 (0.311, 1.080)	
p-值	0.0084		00865	

CI=信賴區間, FOLFOX4 = oxaliplatin + 連續靜脈輸注 5-FU/FA, ORR = 客觀反應率（完全反應及部分反應之患者），OS=存活期, PFS=疾病無惡化存活期, NE=難以估計。

特別是在具 RAS 突變型之患者中觀察到併用 cetuximab 的負面影響。

- EMR 62 202-007：此隨機分配臨床試驗，針對最近一次以 irinotecan 為基礎治療失敗之轉移性直腸結腸癌患者，比較 Cetuximab 與 irinotecan 合併治療（218 位患者）及 Cetuximab 單一治療使用（111 位患者）。

Cetuximab 與 irinotecan 合併治療比較 cetuximab 單一治療使用，降低 46%疾病惡化率，且明顯增加客觀反應率。此隨機分配臨床試驗，對改善存活期並未達到明顯統計意義。然而，在後續治療中，以 cetuximab 單獨治療組的近 50%患者於疾病惡化後接受 cetuximab 與 irinotecan 合併治療，可能因此影響存活期的差異。

頭頸部鱗狀細胞癌
超過 90%的頭頸部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（人數=211）	放射線單一治療（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=overall survival time 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（人數=222）	化學療法（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=objective response rate 客觀反應率，OS=overall survival time 存活期，PFS=progression-free survival time 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。所研究的病患中，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，其平均分佈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 C_{max}（±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。

在一項第一階段試驗中，對於患有難以治療之實體腫瘤的兒童患者(1-18 歲）給予 cetuximab 合併 irinotecan 治療。這些兒童的藥物動力學結果與成人相當。

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激酶（tyrosine kinase）抑制劑顯示會延緩傷口癒合。

適應症
Erbitux®適用於治療具表皮生長因子受體表現型(EGFR expressing)，RAS 原生型（wild-type）之轉移性直腸結腸癌患者
- 與 FOLFIRI (Folinic acid/ 5-FU/ Irinotecan)合併使用之第一線治療。
- 與 FOLFOX 合併使用之第一線治療。

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。

Erbitux®與 FOLFOX 合併使用於轉移性直腸結腸癌患者之第一線治療的適應症是根據第二期臨床試驗的結果。

禁忌
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 – 不良事件的常用術語標準，=CTCAE）。
Erbitux®與內含 oxaliplatin 之化學治療的合併治療禁用於具 RAS 突變型之轉移性直腸結腸癌患者或其 RAS 突變狀態未知的轉移性直腸結腸癌患者（參見"特別警告和注意事項"）
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 G_1（IgG_1）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。

目前尚無 cetuximab 對人類生育力影響的資料。正式的動物試驗中，未曾對雄性及雌性動物的生育力做過評估。

特別警告和注意事項
輸注相關(包括過敏性 anaphylactic)反應
可能會發生嚴重的輸注相關反應(包括過敏反應)，在一些病例會致命。發生嚴重輸注相關反應時，要立即且永遠終止 cetuximab 的治療，可能還需要緊急治療。這些反應有可能是過敏性休克或類過敏性休克反應，或者代表細胞因子釋放症候群（Cytokine Release Syndrome）。症狀可能在第一次輸注期間及數小時後發生、或發生在後續輸注中。建議提醒患者有這一種延遲表現的可能，同時要指示患者如果發生輸注相關反應的徵候或症狀，要聯絡他們的醫師。症狀可能包括支氣管痙攣、蕁麻疹、血壓升高或降低、失去意識或休克。在罕見的個案中，曾發現猝心症、心肌梗塞或心跳停止。
過敏反應(anaphylactic reactions)可能在第一次輸注的幾分鐘內就發生，例如由於已存在的(preformed) IgE 抗體與 cetuximab 交叉反應。這些反應常伴有支

氣管痙攣和蕁麻疹。健管事先給藥預防，仍可能會發生。
有對紅肉或扁蝨叮咬過敏之病史，或對抗 cetuximab 的 IgE 抗體（α-1-3-半乳糖）試驗結果呈陽性的患者，發生過敏反應的風險大大提高。在這些患者，需經過仔細評估過效益/風險(包括替代療法)，並且只有在訓練有素的人員嚴密監督，且備妥急救設備的情況下，方可給予 cetuximab。
首次劑量應緩慢給藥，速率不得超過 5 毫克/分鐘（mg/min），同時嚴密監控所有的生命徵象至少兩小時。如果在第一次輸注時，輸注相關反應在頭 15 分鐘內發生，應停止輸注。應該仔細評估效益/風險，包括考慮患者是否可能已存在 IgE 抗體後，才能給予後續輸注。
如果輸注相關反應在稍後的輸注過程中或後續輸注時發生，進一步的處理將取決於其嚴重程度：
a）第 1 級：在嚴密監督下繼續緩慢輸注
b）第 2 級：繼續緩慢輸注，並且立即施行症狀治療
c）第 3 和 4 級：立即停止輸注，積極治療症狀並禁止後續使用 cetuximab

細胞因子釋放症候群（CRS）通常會發生於輸注後一小時內，並且較少伴有支氣管痙攣和蕁麻疹。CRS 通常在第一次輸注最嚴重。

輕度或中度輸注相關反應極為常見，其症狀包括發熱、寒顫、頭暈、或呼吸困難，其發生主要與第一次輸注有緊密的時間關係。如果患者發生輕度或中度輸注相關反應，可以降低輸注速率。建議後續的輸注都要維持這種較低的輸注速率。
必須密切監測患者，特別是在第一次給藥時。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® 曾有引起間質性肺部疾病的個案報告，這些患者大多為日本人。如果經診斷為間質性肺疾病病，需停止使用 Erbitux® 並且給予患者適當的治療。

皮膚反應
Cetuximab 主要的不良反應為皮膚反應，可能會變得嚴重，特別是在併用化療時。且增加次發性感染(主要是細菌性)的風險和曾通報葡萄球菌脫皮症、壞死性筋膜炎與敗血症病例及致死的病例。
皮膚反應非常常見，且可能需要中斷或停止治療。根據臨床診療指引可考慮預防性給藥以及口服四環黴素(tetracyclines)（6 到 8 週)與外用類固醇藥膏(1% hydrocortisone)和潤膚乳。中效到強效的類固醇藥膏(corticosteroids) 或口服四環黴素被使用來治療皮膚反應。詳細資訊請參閱臨床診療指引。

如果患者出現不能耐受或嚴重皮膚反應（第 3 級；美國國家癌症機構 –不良事件的常用術語標準，CTCAE），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，在重新開始治療時可能無需調整其劑量。
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：200 mg/m² 體表面積，第三次發作：150 mg/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，因腹瀉導致之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電解質補充。

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，曾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。

心血管疾病
在非小細胞肺癌、頭頸部鱗狀細胞癌及直腸結腸癌之治療時，曾被觀察到嚴重有時致死的心血管事件發生頻率會增加，以及曾出現治療猝死的個案。某些臨床研究顯示與患者年齡 65 歲或以上者有關。當處方爾必得舒，並同時投予具心臟毒性成分（例如: fluoropyrimidines）時，患者的心血管狀況及日常體能狀態須被納入考慮。

眼睛疾患
曾有使用 cetuximab 治療出現角膜炎及潰瘍性角膜炎的報告。若患者出現疑似角膜炎的症狀及徵兆，建議諮詢眼科醫師。
若經診斷確定為角膜炎，應審慎考量繼續治療的利益與風險。若確診為潰瘍性角膜炎，則 cetuximab 必須中斷治療或停藥。
曾患過角膜炎、潰瘍性角膜炎或嚴重乾眼症的患者使用時應特別小心。

直腸結腸癌併有 RAS 突變型腫瘤
Erbitux® 不可用來治療其腫瘤有 RAS 突變型或 RAS 腫瘤狀況未知的直腸結腸癌患者，在臨床研究顯示對於 RAS 突變型的腫瘤沒有療效。在臨床研究特別指出 cetuximab 併用 FOLFOX4 對這些患者的無惡化存活期(PFS)和存活期(OS)有負面影響(見"特性")。

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。
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。
兒童患者
Cetuximab 用於年齡小於 18 歲之兒童患者的療效尚未確定。第一期臨床試驗的報告中，並未出現新的兒童患者使用之安全性問題。

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）
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）
"＊"是代表在表格後對其副作用有詳細說明。

神經系統障礙	
常見	頭痛
頻率不明	無菌性腦膜炎
視覺障礙	
常見	結膜炎
不常見	瞼緣炎、角膜炎
呼吸、胸腔及橫隔障礙	
不常見	肺栓塞
罕見	間質性肺病
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*
非常罕見	Stevens-Johnson 症候群/毒性表皮壞死溶解症
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*；在某些個案中可能會出現嚴重之黏膜炎，黏膜炎可能導致鼻出血
常見	嚴重輸注相關反應*、疲勞
肝膽障礙	
非常常見	肝臟酵素值增加（ASAT、ALAT、AP）

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/或較少發生的搔癢、皮膚乾燥、皮膚脫屑、多毛症或指甲病變(例如甲滿炎)。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，只要依循建議調整劑量，停止治療後，皮膚反應總是能緩解，且沒有後遺症。
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、壞死性筋膜炎或敗血症。

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，嚴重白血球減少或嗜中性白血球減少，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 fluoropyrimidines 合併使用時，心臟局部缺血的症狀包括心肌梗塞、充血性心衰竭及手足症候群（手足皮膚紅斑、感覺異常）的發生頻率較 fluoropyrimidines 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特性都沒有改變。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。

用法用量
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輸注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。
首次劑量應緩慢給藥，輸注速率不可超過 5 毫克/分。

直腸結腸癌
Erbitux® 與化學治療合併使用於治療轉移性之直腸結腸癌患者(見"特性")。
開始用 Erbitux® 的治療之前，必須確定是 RAS（KRAS 和 NRAS）原生型。突變狀態應該由有經驗的實驗室使用確效之方法檢測 KRAS exon 2,3,4 和 NRAS exon 2,3,4 的突變來確定（見"特性"和"特別警告和注意事項"）。
併用化學治療藥物的劑量或建議調整劑量，參閱其相關之個別產品資訊。必須在輸注 cetuximab 一小時之後，才能給予後續之化學療法。
建議持續 cetuximab 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"部分所提到的之外），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）。
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
每一個藥瓶中有 20 毫升供輸注用溶液。
單瓶盒裝。

資料日期
2017 年 3 月

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Merck KGaA
Frankfurter Strasse 250, D-64293 Darmstadt, Germany

主製造廠 2
Boehringer Ingelheim Pharma GmbH & Co.KG
Birkendorfer Strasse 65, 88397 Biberach An Der Riss, Germany

包裝廠
Merck KGaA
Frankfurter Strasse 250, D-64293 Darmstadt, Germany

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MerckSerono

MERCK

Erbitux® 5 mg/ml Solution for infusion

Active ingredient: Cetuximab

Composition
Each ml of the solution for infusion contains 5 mg cetuximab as active substance. Each vial contains 20 ml.
Excipients: sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide, water for injection.

Properties
Mechanism of action
The Epidermal Growth Factor Receptor (EGFR) is part of signalling pathways involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Cetuximab is a chimeric monoclonal IgG, antibody that is specifically directed against the EGFR. It binds to the EGFR with an approximately 5- to 10fold higher affinity than endogenous ligands and blocks the receptor's function. It induces the internalisation of EGFR and may thereby lead to down regulation of EGFR. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells (antibody dependent cell-mediated cytotoxicity, ADCC).
Cetuximab does not bind to other receptors belonging to the HER family. The protein product of the proto-oncogene RAS (rat sarcoma) is a central down-stream signal-transducer of EGFR. In tumours, activation of RAS by EGFR contributes to EGFR-mediated increased proliferation, survival and the production of pro-angiogenic factors.
RAS is one of the most frequently activated family of oncogenes in human cancers. Mutations of RAS genes at certain hot-spots on exons 2, 3 and 4 result in constitutive activation of RAS proteins independently of EGFR signalling.

Pharmacodynamic effects
Cetuximab inhibits the proliferation of human tumour cells that express EGFR and induces apoptosis. It also inhibits the production of angiogenic factors, blocks endothelial cell migration and causes a reduction in tumour neo-vascularisation and metastasis.

Colorectal cancer
A diagnostic assay (EGFR pharmDx™) was used for immunohistochemical detection of EGFR expression in tumour material. Approximately 75% of the patients with metastatic colorectal cancer screened for clinical studies had an EGFR-expressing tumour and were therefore considered eligible for cetuximab treatment. The efficacy and safety of cetuximab have not been documented in patients with tumours where EGFR was not detected.
Study data demonstrate that patients with metastatic colorectal cancer and activating RAS mutations are highly unlikely to benefit from treatment with cetuximab or a combination of cetuximab and chemotherapy and as add-on to FOLFOX4 a significant negative effect on progression-free survival time (PFS) was shown.
Further post-hoc analyses were performed for studies EMR 62 202-013 and EMR 62 202-047, where also mutations on RAS genes (NRAS and KRAS) other than KRAS exon 2 have been determined. Only in study EMR 62 202-007, a post-hoc analysis was not possible.

Cetuximab in combination with chemotherapy
- EMR 62 202-013: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and irinotecan plus infusional 5-fluorouracil/folinic acid (FOLFIRI) (599 patients) to the same chemotherapy alone (599 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 63%. For the assessment of the RAS status, mutations other than those on exon 2 of the KRAS gene were determined from all evaluable tumour samples within the KRAS exon 2 wild-type population. The RAS mutant population consists of patients with known KRAS exon 2 mutations as well as additionally identified RAS mutations.

The efficacy data generated in this study are summarised in the table below:

Variable/statistic	RAS wild-type population		RAS mutant population	
	Cetuximab plus FOLFIRI	FOLFIRI	Cetuximab plus FOLFIRI	FOLFIRI
	(N=178)	(N=189)	(N=246)	(N=214)
OS				
months, median	28.4	20.2	16.4	17.7
(95% CI)	(24.7, 31.6)	(17.0, 24.5)	(14.9, 18.4)	(15.4, 19.6)
Hazard Ratio (95% CI)	0.691 (0.543, 0.879)		1.049 (0.860, 1.281)	
p-value	0.0024		0.6355	
PFS				
months, median	11.4	8.4	7.4	7.5
(95% CI)	(10.0, 14.6)	(7.4, 9.4)	(6.4, 8.0)	(7.2, 8.5)
Hazard Ratio (95% CI)	0.556 (0.406, 0.761)		1.098 (0.852, 1.415)	
p-value	0.0002		0.4696	
ORR				
%	66.3	38.6	31.7	36.0
(95% CI)	(58.8, 73.2)	(31.7, 46.0)	(25.9, 37.9)	(29.6, 42.8)
Odds ratio (95% CI)	3.1145 (2.0279, 4.7835)		0.8478 (0.5767, 1.2462)	
p-value	<0.0001		0.3970	

CI = confidence interval, FOLFIRI = irinotecan plus infusional 5- fluorouracil/folinic acid ORR = objective response rate (patients with complete response or partial response), OS = overall survival time, PFS = progression-free survival time The proportion of KRAS-evaluable subjects in the overall population was 88.7% (1063 of 1198 subjects)

In the overall population the addition of cetuximab to irinotecan plus infusional 5-fluorouracil/folinic acid (FOLFIRI) significantly improved median overall survival time (19.9 vs. 18.6 months; p=0.0420; HR 0.878), median progression free survival time (8.9 vs. 8.0 months; p=0.0479; HR 0.851) and objective response rate (46.9% vs. 38.7 %; p=0.0038).
- EMR 62 202-047: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and oxaliplatin plus continuous infusional 5-fluorouracil/folinic acid (FOLFOX4) (169 patients) to the same chemotherapy alone (168 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 57%. For the assessment of the RAS status, mutations other than those on exon 2 of the KRAS gene were determined from all evaluable tumour samples within the KRAS exon 2 wild-type population. The RAS mutant population consists of patients with known KRAS mutations as well as additionally identified RAS mutations.

The efficacy data generated in this study are summarised in the table below:

Variable/statistic	RAS wild-type population		RAS mutant population	
	Cetuximab plus FOLFOX4	FOLFOX4	Cetuximab plus FOLFOX4	FOLFOX4
	(N=38)	(N=49)	(N=92)	(N=75)
OS				
months, median	19.8	17.8	13.5	17.8
(95% CI)	(16.6, 25.4)	(13.8, 23.9)	(12.1, 17.7)	(15.9, 23.6)
Hazard Ratio (95% CI)	0.937 (0.563, 1.558)		1.291 (0.905, 1.842)	
p-value	0.8002		0.1573	
PFS				
months, median	12.0	5.8	5.6	7.8
(95% CI)	(5.8, NE)	(4.7, 7.9)	(4.4, 7.5)	(6.7, 9.3)
Hazard Ratio (95% CI)	0.533 (0.272, 1.042)		1.541 (1.037, 2.289)	
p-value	0.0615		0.0309	
ORR				
%	57.9	28.6	37.0	50.7
(95% CI)	(40.8, 73.7)	(16.6, 43.3)	(27.1, 47.7)	(38.9, 62.4)
Odds ratio (95% CI)	3.3302 (1.375, 8.172)		0.580 (0.311, 1.080)	
p-value	0.0084		0.0865	

CI = confidence interval, FOLFOX4 = oxaliplatin plus continuous infusional 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), OS = overall survival time, PFS = progression-free survival time, NE = not estimable

In particular a negative effect of cetuximab add-on in the RAS mutant population was observed.
- EMR 62 202-007: This randomised study in patients with metastatic colorectal cancer after failure of irinotecan-based treatment for metastatic disease as the last treatment before study entry compared the combination of cetuximab and irinotecan (218 patients) with cetuximab monotherapy (111 patients).

The combination of cetuximab with irinotecan compared to cetuximab alone reduced the overall risk of disease progression by 46% and significantly increased the objective response rate. In the randomised trial, the improvement in overall survival time did not reach statistical significance; however, in the follow-up treatment, nearly 50% of the patients of the cetuximab alone arm received a combination of cetuximab and irinotecan after progression of disease, which may have influenced overall survival time.

Squamous cell cancer of the head and neck
Immunohistochemical detection of EGFR expression was not performed since more than 90% of patients with squamous cell cancer of the head and neck have tumours that express EGFR.

Cetuximab in combination with radiation therapy for locally advanced disease
- EMR 62 202-006: This randomised study compared the combination of cetuximab and radiation therapy (211 patients) with radiation therapy alone (213 patients) in patients with locally advanced squamous cell cancer of the head and neck. Cetuximab was started one week before radiation therapy and administered until the end of the radiation therapy period.

The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	Radiation therapy + cetuximab (N=211)		Radiation therapy alone (N=213)	
Locoregional control				
months, median (95% CI)	24.4	(15.7, 45.1)	14.9	(11.8, 19.9)
Hazard Ratio (95%CI)	0.68 (0.52, 0.89)			
p-value	0.005			
OS				
months, median (95% CI)	49.0	(32.8, 62.6+)	29.3	(20.6, 42.8)
Hazard Ratio (95%CI)	0.74 (0.56, 0.97)			
p-value	0.032			

CI = confidence interval, OS = overall survival time, a '+' denotes that the upper bound limit had not been reached at cut-off

Patients with a good prognosis as indicated by tumour stage, Karnofsky performance status (KPS) and age had a more pronounced benefit, when cetuximab was added to radiation therapy. No clinical benefit could be demonstrated in patients with KPS ≤ 80 who were 65 years of age or older.
The use of cetuximab in combination with chemo-radiotherapy has so far not been adequately investigated. Thus, a benefit-risk ratio for this combination has not yet been established.

Cetuximab in combination with platinum-based chemotherapy in recurrent and/or metastatic disease
- EMR 62 202-002: This randomised study in patients with recurrent and/or metastatic squamous cell cancer of the head and neck who had not received prior chemotherapy for this disease compared the combination of cetuximab and cisplatin or carboplatin plus infusional 5-fluorouracil (222 patients) to the same chemotherapy alone (220 patients). Treatment in the cetuximab arm consisted of up to 6 cycles of platinum-based chemotherapy in combination with cetuximab followed by cetuximab as maintenance therapy until disease progression.

The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	Cetuximab + CTX (N=222)	CTX (N=220)
OS		
months, median (95% CI)	10.1 (8.6, 11.2)	7.4 (6.4, 8.3)
Hazard Ratio (95% CI)	0.797 (0.644, 0.986)	
p-value	0.0362	
PFS		
months, median (95% CI)	5.6 (5.0, 6.0)	3.3 (2.9, 4.3)
Hazard Ratio (95% CI)	0.538 (0.431, 0.672)	
p-value	<0.0001	
ORR		
% (95% CI)	35.6 (29.3, 42.3)	19.5 (14.5, 25.4)
p-value	0.0001	

CI = confidence interval, CTX = platinum-based chemotherapy, ORR = objective response rate, OS = overall survival time, PFS = progression-free survival time

Patients with a good prognosis as indicated by tumour stage, Karnofsky performance status (KPS) and age had a more pronounced benefit, when cetuximab was added to platinum-based chemotherapy. In contrast to progression free survival time, no benefit in overall survival time could be demonstrated in patients with KPS ≤ 80 who were 65 years of age or older.

Immunogenicity
The development of human anti-chimeric antibodies (HACA) is a class-specific effect of monoclonal chimeric antibodies. Measurable HACA titres developed in 3.4% of the patients studied. No conclusive data on the neutralising effect on cetuximab is available to date. The appearance of HACA did not correlate with the occurrence of hypersensitivity reactions or any other undesirable effect to cetuximab.

Pharmacokinetic properties
Intravenous infusions of cetuximab exhibited dose-dependent pharmacokinetics at weekly doses ranging from 5 to 500 mg/m² body surface area. When cetuximab was administered at an initial dose of 400 mg/m² body surface area, the mean volume of distribution was approximately equivalent to the vascular space (2.9 l/m² with a range of 1.5 to 6.2 l/m²). The mean C_{max} (± standard deviation) was 185±55 microgram per ml. The mean clearance was 0.022 l/h per m² body surface area. Cetuximab has a long elimination half-life with values ranging from 70 to 100 hours at the target dose.
Cetuximab serum concentrations reached stable levels after three weeks of cetuximab monotherapy. Mean peak cetuximab concentrations were 155.8 microgram per ml in week 3 and 151.6 microgram per ml in week 8, whereas the corresponding mean trough concentrations were 41.3 and 55.4 microgram per ml, respectively. In a study of cetuximab administered in combination with irinotecan, the mean cetuximab trough levels were 50.0 microgram per ml in week 12 and 49.4 microgram per ml in week 36.
Several pathways have been described that may contribute to the metabolism of antibodies. All of these pathways involve the biodegradation of the antibody to smaller molecules.
An integrated analysis across all clinical studies showed that the pharmacokinetic characteristics of cetuximab are not influenced by race, age, gender, renal or hepatic status.
In a phase I study in paediatric patients (1-18 years) with refractory solid tumours, cetuximab was administered in combination with irinotecan. The pharmacokinetic results were comparable to those in adults.

Non-clinical safety data
Dose-dependent skin alterations, starting at dose levels equivalent to those used in humans, were the major findings in animal toxicity studies. An embryo-foetal toxicity study in Cynomolgus monkeys revealed no signs of teratogenicity. However, dependent on the dose, an increased incidence of abortion was observed.
Non-clinical data on genotoxicity and local tolerance including accidental routes of administration revealed no special hazard for humans.
No formal animal studies have been performed to establish the carcinogenic potential of cetuximab or to determine its effects on male and female fertility.
Toxicity studies with co-administration of cetuximab and chemotherapeutic agents have not been performed.
No non-clinical data on the effect of cetuximab on wound healing are available to date. However, in preclinical wound healing models, EGFR selective tyrosine kinase inhibitors were shown to retard wound healing.

Indication
Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer
- in first-line in combination with FOLFIRI (Folinic acid/5-FU/Irinotecan),
- in first-line in combination with FOLFOX.

Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck
- in combination with radiation therapy for locally advanced disease (Oropharynx, hypopharynx, larynx).
- in combination with platinum-based chemotherapy for recurrent and/ or metastatic disease.

The indication of Erbitux in combination with FOLFOX in first-line treatment of patients with mCRC is based on the results of Phase II study.

Contraindications
Erbitux is contraindicated in patients with known severe (grade 3 or 4; U.S. National Cancer Institute – Common Terminology Criteria for Adverse Events; CTCAE) hypersensitivity reactions to cetuximab.
The combination of Erbitux with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant RAS metastatic colorectal cancer (mCRC) or for whom RAS mCRC status is unknown (see also 'Special warnings and precautions')
Before initiation of combination treatment, contraindications for concomitantly used chemotherapeutic agents or radiation therapy must be considered.

Pregnancy and lactation
EGFR is involved in foetal development. Limited observations in animals are indicative of a placental transfer of cetuximab, and other IgG, antibodies have been found to cross the placental barrier. Animal data revealed no evidence of teratogenicity. However, dependent on the dose, an increased incidence of abortion was observed. Sufficient data from pregnant women are not available.
It is strongly recommended that Erbitux be given during pregnancy or to any woman not employing adequate contraception only if the potential benefit justifies a potential risk for the foetus.
It is recommended that women do not breast-feed during treatment with Erbitux and for two months after the last dose, because it is not known whether Erbitux is excreted in breast milk.
There are no data on the effect of cetuximab on human fertility. Effects on male and female fertility have not been evaluated within formal animal studies.

Special Warnings and Precautions
Infusion-related, including anaphylactic, reactions
Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a cytokine release syndrome (CRS). Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. It is recommended to warn patients of the possibility of such a late onset and instruct them to contact their physician if symptoms or signs of an infusion-related reaction occur. Symptoms may include bronchospasm, urticaria,

increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.
Anaphylactic reactions may occur as early as within a few minutes of the first infusion e.g. due to preformed IgE antibodies cross-reacting with cetuximab. These reactions are commonly associated with bronchospasm and urticaria. They can occur despite the use of premedication.
The risk for anaphylactic reactions is much increased in patients with a history of allergy to red meat or tick bites or positive results of tests for IgE antibodies against cetuximab (α-1-3-galactose). In these patients cetuximab should be administered only after a careful assessment of benefit/risk, including alternative treatments, and only under close supervision of well trained personnel with resuscitation equipment ready.
The first dose should be administered slowly and the speed must not exceed 5 mg/min whilst all vital signs are closely monitored for at least two hours. If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have preformed IgE antibodies before a subsequent infusion is given.
If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity:
a) Grade 1: continue slow infusion under close supervision
b) Grade 2: continue slow infusion and immediately administer treatment for symptoms
c) Grade 3 and 4: stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab
A cytokine release syndrome (CRS) typically occurs within one hour after infusion nad is less commonly associated with bronchospasm and urticaria. CRS is normally most severe in relation to the first infusion.
Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first cetuximab infusion. If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions.
A close monitoring of patients, particularly during the first administration, is required. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.

Respiratory disorders
Cases of interstitial lung disease have been reported, with the majority of patients from the Japanese population. If interstitial lung disease is diagnosed, Erbitux must be discontinued and the patient be treated appropriately.

Skin reactions
Main adverse reactions of cetuximab are skin reactions which may become severe, especially in combination with chemotherapy. The risk for secondary infections (mainly bacterial) is increased and cases of staphylococcal scalded skin syndrome, necrotising fasciitis and sepsis, in some cases with fatal outcome, have been reported.
Skin reactions are very common and treatment interruption or discontinuation may be required. According to clinical practice guidelines prophylactic use of oral tetracyclines (6-8 weeks) and topical application of 1% hydrocortisone cream with moisturiser should be considered. Medium to high-potency topical corticosteroids or oral tetracyclines have been used for the treatment of skin reactions.
If a patient experiences an intolerable or severe skin reaction (≥ grade 3; US National Cancer Institute – Common Terminology Criteria for Adverse Events; CTCAE), Erbitux therapy must be interrupted. Treatment may only be resumed, if the reaction has resolved to grade 2. If the severe skin reaction occurred for the first time, treatment may be resumed without any change in dose level. With the second and third occurrences of severe skin reactions, Erbitux therapy must again be interrupted. Treatment may only be resumed at a lower dose level (200 mg/m² body surface area after the second occurrence, and 150 mg/m² after the third occurrence), if the reaction has resolved to grade 2.
If severe skin reactions occur a fourth time or do not resolve to grade 2 during interruption of treatment, permanent discontinuation of Erbitux treatment is required.

Electrolyte disturbances
Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Hypomagnesaemia is reversible following discontinuation of Erbitux. In addition, hypokalaemia may develop as a consequence of diarrhoea. Hypocalcaemia may also occur; in particular in combination with platinum-based chemotherapy the frequency of severe hypocalcaemia may be increased.
Determination of serum electrolyte levels is recommended prior to and periodically during Erbitux treatment. Electrolyte repletion is recommended, as appropriate.

Neutropenia and related infectious complications
Patients who receive Erbitux in combination with platinum-based chemotherapy are at an increased risk for the occurrence of severe neutropenia, which may lead to subsequent infectious complications such as febrile neutropenia, pneumonia or sepsis. Careful monitoring is recommended in such patients, in particular in those who experience skin lesions, mucositis or diarrhoea that may facilitate the occurrence of infections.

Cardiovascular disorders
An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed in the treatment of non-small cell lung cancer, squamous cell carcinoma of the head and neck and colorectal carcinoma. In some studies association with age ≥ 65 years has been observed. When prescribing Erbitux, the cardiovascular and performance status of the patients and concomitant administration of cardiotoxic compounds such as fluoropyrimidines should be taken into account.

Eye disorders
Cases of keratitis and ulcerative keratitis have been reported with the use of cetuximab. It is recommended that patients with signs and symptoms suggestive of keratitis consult an ophthalmologist.
If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab must be interrupted or discontinued.
Special attention is recommended for patients with a history of keratitis, ulcerative keratitis or severe dry eye.

Colorectal cancer patients with RAS mutated tumours
Erbitux should not be used in the treatment of colorectal cancer patients whose tumours have RAS mutations or for whom RAS tumour status is unknown. Results from clinical studies show a negative benefit-risk balance in tumours with RAS mutations. In particular, in these patients negative effects on progression-free survival (PFS) and overall survival (OS) were seen as add-on to FOLFOX4 (see Properties).

Combination treatment
When Erbitux is combined with chemotherapeutic agents, also refer to the product information for these medicinal products.
There is limited experience in the use of Erbitux in combination with radiation therapy in colorectal cancer.

Effects on the ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effects subside.

Special populations
Only patients with adequate renal and hepatic function have been investigated to date (serum creatinine ≤ 1.5fold, transaminases ≤ 5fold and bilirubin ≤ 1.5fold the upper limit of normal). Erbitux has not been studied in patients with one or more of the following abnormal laboratory parameters: haemoglobin < 9 g/dl, leukocyte count < 3,000/mm³, absolute neutrophil count < 1,500/mm³, platelet count < 100,000/mm³.
No dose adjustment is required in older people, but the experience is limited in patients 75 years of age and above.

Paediatric population
The efficacy of cetuximab in paediatric patients below the age of 18 years has not been established.
No new safety signals were identified in paediatric patients as reported from a phase-I study.

Adverse effects
Adverse effects listed below may be expected under treatment with Erbitux.
The following definitions apply to the frequency terminology used hereafter:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Frequency not known (cannot be estimated from the available data)
An asterisk (*) indicates that additional information on the respective undesirable effect is provided below the table.

Nervous system disorders
Common: Headache.
Frequency not known: Aseptic meningitis.

Eye disorders
Common: Conjunctivitis.
Uncommon: Blepharitis, keratitis.

Respiratory, thoracic and mediastinal disorders
Uncommon: Pulmonary embolism.
Rare: Interstitial lung disease.

Gastrointestinal disorders
Common: Diarrhoea, nausea, vomiting.

Skin and subcutaneous tissue disorders
Very common: Skin reactions*.
Frequency not known: Superinfection of skin lesions*.
Very rare: Stevens-Johnson syndrome/toxic epidermal necrolysis.

Metabolism and nutrition disorders
Very common: Hypomagnesaemia.
Common: Dehydration, in particular secondary to diarrhoea or mucositis; hypocalcaemia; anorexia which may lead to weight decrease.

Vascular disorders
Uncommon: Deep vein thrombosis.

General disorders and administration site conditions
Very common: Mild or moderate infusion-related reactions*; mucositis, in some cases severe. Mucositis may lead to epistaxis.
Common: Severe infusion-related reactions*, fatigue.

Hepatobiliary disorders
Very common: Increase in liver enzyme levels (ASAT, ALAT, AP).

Additional information
Overall, no clinically relevant difference between genders was observed.

Infusion-related reactions
Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first Erbitux infusion.
Severe infusion-related reactions may commonly occur, in rare cases with fatal outcome. They usually develop during or within 1 hour of the initial Erbitux infusion, but may occur after several hours or with subsequent infusions. Although the underlying mechanism has not been identified, some of these reactions may be anaphylactoid/anaphylactic in nature and may include symptoms such as bronchospasm, urticaria, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.
For clinical management of infusion-related reactions, see 'Special warnings and precautions'.

Skin reactions
Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g. paronychia). Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. The majority of skin reactions develop within the first three weeks of therapy. They generally resolve, without sequelae, over time following cessation of treatment if the recommended adjustments in dose regimen are followed.
Skin lesions induced by Erbitux may predispose patients to superinfections (e.g. with *S. aureus*), which may lead to subsequent complications, e.g. cellulitis, erysipelas, or, potentially with fatal outcome, staphylococcal scalded skin syndrome, necrotising fasciitis or sepsis.

Combination treatment
When Erbitux is used in combination with chemotherapeutic agents, also refer to their respective product information.
For adverse effects in combination with other chemotherapeutic agents please see 'Interactions'.
In combination with local radiation therapy of the head and neck area, additional undesirable effects were those typical of radiation therapy (such as mucositis, radiation dermatitis, dysphagia or leukopenia, mainly presenting as lymphocytopenia). In a randomised controlled clinical study with 424 patients, reporting rates of severe acute radiation dermatitis and mucositis as well as of late radiation-therapy-related events were slightly higher in patients receiving radiation therapy in combination with Erbitux than in those receiving radiation therapy alone.

Interactions
In combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis compared to platinum-based chemotherapy alone (see also 'Special warnings and precautions').
In combination with fluoropyrimidines, the frequency of cardiac ischaemia including myocardial infarction and congestive heart failure as well as the frequency of hand-foot syndrome (palmar-plantar erythrodysaesthesia) were increased compared to that with fluoropyrimidines.
A formal interaction study with irinotecan in humans showed unchanged pharmacokinetics of both drugs when used in combination. Clinical data showed no influence on the safety-profile of Erbitux. No other formal interaction studies have been performed with Erbitux in humans.

Dosage and Administration
Erbitux must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion time and for at least 1 hour after the end of the infusion. Resuscitation equipment must be available.
Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions.
In all indications, Erbitux is administered once a week. The very first dose is 400 mg Erbitux per m² body surface area with a recommended infusion period of 120 minutes. All subsequent weekly doses are 250 mg per m² body surface area each with a recommended infusion period of 60 minutes. The maximum infusion rate must not exceed 10 mg/min. The initial dose should be given slowly and speed of infusion must not exceed 5mg/min.

Colorectal cancer
In patients with metastatic colorectal cancer, Erbitux is used in combination withchemotherapy (see 'Properties').Evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with Erbitux. Mutational status should be determined by an experienced laboratory using validated test methods for detection of KRAS and NRAS (exons 2, 3, and 4) mutations (see 'Properties' and 'Special warnings and precautions').
For the dosage or recommended dose modifications of concomitantly used -chemotherapeutic agents, refer to the product information for these medicinal products. They must not be administered earlier than 1 hour after the end of the cetuximab infusion.
It is recommended that cetuximab treatment be continued until progression of the underlying disease.

Squamous cell cancer of the head and neck
In patients with locally advanced squamous cell cancer of the head and neck, Erb is used concomitantly with radiation therapy. It is recommended to start Erbi therapy one week before radiation therapy and to continue Erbitux therapy until ti end of the radiation therapy period.
In patients with recurrent and/or metastatic squamous cell cancer of the head ano neck, Erbitux is used in combination with platinum-based chemotherapy followed by Erbitux as maintenance therapy until disease progression. Chemotherapy must not be administered earlier than 1 hour after the end of the Erbitux infusion.

Instructions for use and handling
Erbitux 5 mg/ml is administered intravenously with an infusion pump, gravity drip or a syringe pump. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride 9 mg/ml (0.9%) solution for injection at the end of infusion. Erbitux 5 mg/ml is a colourless solution.
Erbitux 5 mg/ml is compatible with:
- PE (polyethylene), EVA (ethyl vinyl acetate) or PVC (polyvinyl chloride) bags,
- PE, EVA, PVC, TP (polyolefine thermoplast) or PUR (polyurethane) infusion sets,
- PP (polypropylene) syringes for syringe pump.

Erbitux does not contain any antimicrobial preservative or bacteriostatic agent. Therefore, aseptic handling must be ensured when preparing the infusion. Immediate use after opening is strongly recommended.
Erbitux 5 mg/ml must be prepared as follows:
For administration with infusion pump or gravity drip (diluted with sterile sodium chloride 9 mg/ml (0.9%) solution): Take an infusion bag of adequate size of sterile sodium chloride 9 mg/ml (0.9%) solution. Calculate the required volume of Erbitux. Remove an adequate volume of the sodium chloride solution from the infusion bag, using an appropriate sterile syringe with a suitable needle. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Transfer Erbitux into the prepared infusion bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with the diluted Erbitux before starting the infusion. Use a gravity drip or an infusion pump for administration. Set and control the rate as explained above.
For administration with infusion pump or gravity drip (undiluted): Calculate the required volume of Erbitux. Take an appropriate sterile syringe (minimum 50 ml) and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Transfer Erbitux into a sterile evacuated container or bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with Erbitux before starting the infusion. Use a gravity drip or an infusion pump for administration. Set and control the rate as explained above.
For administration with a syringe pump: Calculate the required volume of Erbitux. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Remove the needle and put the syringe into the syringe pump. Connect the infusion line to the syringe, set and control the rate as explained above and start the infusion after priming the line with Erbitux or sterile sodium chloride 9 mg/ml (0.9%) solution. If necessary, repeat this procedure until the calculated volume has been infused.

Incompatibilities
Erbitux 5 mg/ml must not be mixed with other intravenously applied medicinal products, except those mentioned above in section 'Instructions for use and handling'. A separate infusion line must be used.

Overdose
There is limited experience with single doses higher than 400 mg/m² body surface area to date or weekly administrations of doses higher than 250 mg/m² body surface area.

Storage and Stability
Store in a refrigerator (2°C – 8°C).
Do not use after the expiry date.

Keep medicines out of the reach of children.
Chemical and physical in-use stability of Erbitux 5 mg/ml has been demonstrated for 48 hours at 25°C, if the solution is prepared as described above.
Erbitux does not contain any antimicrobial preservative or bacteriostatic agent. Use immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C.

Presentation
20 ml of solution for infusion in a vial.
One vial per pack.

Date of Information
Mar, 2017

Manufacturer 1
Merck KGaA
Frankfurter Strasse 250, D-64293 Darmstadt, Germany

Manufacturer 2
Boehringer Ingelheim Pharma GmbH & Co.KG
Birkendorfer Strasse 65, 88397 Biberach An Der Riss, Germany

Packaging Site
Merck KGaA
Frankfurter Strasse 250, D-64293 Darmstadt, Germany

仿單標籤粘貼表

產品名稱	爾必得舒注射液 5 毫克／毫升	申請廠商	台灣默克股份有限公司
衛生福利部 食品藥物管理署給證號碼	衛署菌疫輸字第 000877 號		

106.0214

ERBITUX 5 mg/ml
solution for infusion
1 vial of
20 ml

7802371344

ERBITUX 5 mg/ml
solution for infusion
1 ml contains 5 mg cetuximab.
Sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide, water for injection.

4 710784 853063

Erbitux® is a trademark of ImClone LLC

ERBITUX 5 mg/ml
solution for infusion
Cetuximab

1 vial of
20 ml

MERCK

ERBITUX 5 mg/ml
solution for infusion
Intravenous use.
Read enclosed leaflet before use.
Keep out of the reach and sight of children.
Store in a refrigerator (2°C-8°C).
Medicinal product subject to medical prescription.
Merck KGaA
Frankfurter Strasse 250
D-64293 Darmstadt
Germany

ERBITUX 5 mg/ml
solution for infusion
爾必得舒®
注射液 5毫克/毫升
衛署菌疫輸字第000877號
本藥限由醫師使用
製造廠:Merck KGaA
廠 址:Frankfurter Strasse 250,
D-64293 Darmstadt, Germany
藥 商:台灣默克股份有限公司
地 址:台北市內湖區堤頂大道二段89號6樓
電 話:(02)2162-1111

MerckSerono

80-0208
42 x 42 x 90

EXP:
Batch No.:
MFD:

ERBITUX 5 mg/ml 20 ml
MerckSerono
solution for infusion
爾必得舒®
注射液 5毫克/毫升
Cetuximab
Intravenous use
Read enclosed leaflet before use.
Store in a refrigerator (2°C - 8°C).
Merck KGaA (Office)
Frankfurter Strasse 250
D-64293 Darmstadt, Germany
7862371343
Batch No.:
MFD:
EXP:
MERCK

4 710784 853063

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