

National PBM Drug Monograph
Cetuximab (Erbix™)
September 2004

VA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Efficacy:

1. A chimeric monoclonal antibody against the Epidermal Growth Factor Receptor. EGFR is over expressed in metastatic colorectal cancers.
2. Blockade of the receptor causes internalization and down regulation of the receptor resulting in reduced proliferation, increased apoptosis, inhibition of factors associated with angiogenesis, and inhibition of cell adhesion.
3. Cetuximab monotherapy cetuximab plus irinotecan was evaluated in patients who progressed during therapy or within 3 months of stopping irinotecan therapy (as first or second-line therapy) in patients with colorectal cancers. Combination therapy resulted in PR's in 23% with a time to progression of 4.1 months. Monotherapy resulted in PR's in 11% with a time to progression of 1.5 months.
4. Preliminary data in head and neck cancer in combination with either radiation or cisplatin showed good response rates, time to progression, and overall survival compared to the same treatment without cetuximab.
5. EGFR expression did not correlate significantly with tumor response. The development of a rash appears to predict higher rates of response.
6. Approved indications: Combination therapy with irinotecan for treatment of metastatic colorectal cancers in patents with EGFR positive tumors refractory to irinotecan-based therapy. Monotherapy is indicated for use in patients who are unable to tolerate irinotecan;
7. Dose: Loading dose of 400mg/m² followed by weekly dose of 250mg/m².

Safety:

1. Most common adverse events: acneform rash, leukopenia, asthenia, diarrhea, nausea, vomiting, abdominal pain.
2. Most serious adverse events: acneform rash/dermatologic reactions, diarrhea and dehydration, interstitial lung disease, fever, pulmonary embolus, infusion reactions, sepsis, kidney failure.
3. Dose modifications are recommended for infusion reactions and for acneform rash.
4. Rash should be monitored for co-existing infection that may necessitate topical or oral antibiotics.

Conclusions

1. Cetuximab plus irinotecan resensitizes some tumor cells to irinotecan.
2. The registration trial was powered for response rate but not time to progression or overall survival.
3. Monotherapy produced little benefit in irinotecan refractory patients.
4. There are many unanswered questions about the patient populations that would benefit most from this therapy.

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Introduction

The purpose of this monograph is to review the clinical efficacy and safety of the IgG monoclonal antibody cetuximab, which binds to the Epidermal Growth Factor Receptor (EGFR). EGFR expression and/or up regulation occurs in 60-80% of colorectal carcinomas.

Pharmacology/Pharmacokinetics¹

Cetuximab is a chimeric monoclonal IgG antibody with a high affinity for the EGFR. The naturally occurring receptor ligand EGF is important for cell proliferation, inhibition of apoptosis, angiogenesis, and metastasis. The antitumor effect of cetuximab is thought to be due to blockade of the receptor from its natural ligand, internalization and down-regulation of the receptor, reduction in proliferation, increased apoptosis, inhibition of autocrine factors associated with angiogenesis, and inhibition of tumor cell invasion by inhibiting molecules with a key role in tumor cell adhesion. In addition, cetuximab has shown additive effects with irinotecan, topotecan, VEGF inhibitors, and as a radiosensitizer in carcinoma cell lines and in murine models.

	Cetuximab
Metabolism	N/A
Elimination	N/A
Half-life	72 to 96 hours
Protein Binding	N/A

Clearance of cetuximab occurs primarily through binding to the EGFR receptor that then internalizes the antibody-receptor complex. Clearance is non-linear and decreases with increasing dose, suggesting saturation of the metabolic pathway

FDA Approved Indication(s) and Off-label Uses

Cetuximab in combination with irinotecan is indicated for treatment of metastatic colorectal cancers that express EGFR and are refractory to irinotecan-based therapy.

Single agent cetuximab is indicated for treatment of metastatic colorectal cancers that express EGFR in patients intolerant to irinotecan therapy.

Off label uses: in combination with radiotherapy for locoregionally advanced squamous cell carcinoma of the head and neck, in combination with chemotherapy for head and neck cancers, non-small cell lung cancer, and pancreatic cancer.

Dosage and Administration

The recommended dose is 400mg/m² as an initial loading dose over 120 minutes (maximum 5ml/min). Weekly maintenance doses are 250mg/m² over 60 minutes.

Special patient populations – Clinical trials in special populations (hepatic or renal impairment or pediatric patients) have not been conducted. Population pharmacokinetics have been explored and suggest that dose modifications are not needed in these populations. Females had a 25% lower clearance but similar efficacy and safety as male patients.

Dose Modifications

Infusion Reaction	Dose Modification
Mild or Moderate (Grade 1 or 2)	Permanently reduce dose 50%
Severe (Grade 3 or 4)	Immediately and permanently discontinue

Dermatologic Toxicities: No dose modifications are needed for mild or moderate skin toxicity

Severe Dermatologic Toxicity

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

Preparation for administration

Cetuximab should always be administered using a **low protein 0.22micron in-line filter**

Cetuximab solution (100mg/50ml = 2mg/ml) should be clear and colorless but may contain small visible white cetuximab particulates. The solution should NOT be shaken or diluted. It may be administered by an infusion pump (using an evacuated container) or by syringe pump. The line may be flushed with 0.9% sodium chloride after the infusion.

Patients should be observed for 1 hour following the cetuximab infusion for signs of an infusion reaction.

Efficacy Measures

Primary Outcome: Objective response to cetuximab + irinotecan and cetuximab monotherapy in EGFR positive irinotecan refractory metastatic colorectal cancer.

Secondary Outcomes: Time to Progression (TTP)
 Time to Treatment Failure (TTF)
 Disease Control Rate
 Duration of Response
 Overall Survival
 Safety

Clinical Trials^{2,3}

Pivotal Registration Trial

Bowel Oncology with Cetuximab Antibody (BOND): Open, randomized, multicenter, phase II trial of cetuximab alone or in combination with irinotecan in patients with EGFR positive irinotecan refractory metastatic colorectal adenocarcinomas.

Efficacy Parameter	Number (%) of Patients		p-value
	Cetuximab + irinotecan (N=218)	Cetuximab (N=111)	
Complete Response (CR)	0 (0.0)	0 (0.0)	
Partial Response (PR)	50 (22.9)	12 (10.8)	
Stable Disease (SD)	71 (32.6)	24 (21.6)	
Progressive Disease	68 (31.2)	59 (53.2)	
Objective Response (CR+PR)	50 (22.9)	12 (10.8)	0.007
Disease Control (CR+PR+SD)	121 (55.5)	36 (32.4)	0.0001
Overall Survival			
Median Survival (months)	8.6	6.9	
Estimated 1-year survival	29%	32%	
Mean TTP (months)	4.1	1.5	<0.001
Hazard Ratio	0.54 (95%CI 0.42,0.71)		<0.001

Eligibility: Stage IV colorectal carcinoma, a Karnofsky performance status of 60 or more, adequate hematologic, renal, and liver function, received one of several prestudy irinotecan regimens for at least six weeks and documentation of progression during therapy or within 3 months thereafter (independently confirmed by a committee blinded to treatment assignment), evidence of EGFR expression in primary tumor or in at least one metastases.

Dose: Cetuximab was given at an initial dose of 400mg/m² followed by weekly infusions of 250mg/m², preceded by an H1 blocker. Patients assigned to the combination therapy group received irinotecan at the same dose and schedule as given during their most recent prestudy therapy.

Primary Endpoint: Rate of confirmed radiologic tumor response. The sample size was powered for the estimation of the confidence interval expected for the combination group based on a response rate of 19%.

Results: The objective response rate (CR+PR) in irinotecan-refractory patients receiving combination therapy was 22.9%, with a median duration of response of 5.7 months. In patients receiving monotherapy, the objective response rate was 10.8% with a duration of response of 4.2 months. Responses were similar in the cohort of patients who received oxaliplatin in addition to irinotecan before entering. The degree of EGFR expression (either % of EGFR positive cells or staining intensity) did not significantly correlate with clinical response; patients whose tumors did not express any EGFR were excluded from the study. Response rates in patients with skin reactions were higher than those without skin reactions (25.8% vs 6.3 percent in the combination group). Fifty-six patients in the monotherapy group received additional irinotecan upon progression producing PR in 3.6% and stable disease in 36%. The median number of infusions of cetuximab was 18 in the combination group and 7 in the monotherapy group.

Subpopulation: Irinotecan and Oxaliplatin Failures

Efficacy Parameter	Number (%) of Patients		p-value
	Cetuximab + Irinotecan (N=80)	Cetuximab (N=44)	
Objective Response Rate	19 (23.8)	5 (11.4)	0.09
Disease Control Rate	43 (53.8)	14 (31.8)	0.024
Median Overall Survival (months)	7.9	7.0	
Median TTP (months)	2.9	1.5	<0.001

Supportive Trials

Trial	Inclusion/Exclusion	Objectives	Results								
IMCL 9923 Phase II Open-label, NR, MC N=139 (121PD + 18SD) Cetuximab: 400mg/m ² initial dose then 250mg/m ² weekly plus irinotecan on previous schedule	1. EGFR+ colorectal carcinoma 2. Stable disease, &received at least 12 weeks of irinotecan OR Progressive disease at any time after receiving irinotecan	Primary: ORR Secondary: TTP Safety QoL EGFR expression OS	<table border="1"> <thead> <tr> <th>Outcome</th> <th>Percent</th> </tr> </thead> <tbody> <tr> <td>ORR (CR+PR) All (N=138) Irinotecan refractory (N=74)</td> <td>15 12</td> </tr> <tr> <td>Median OS (months)</td> <td>8.4</td> </tr> <tr> <td>Median TTP(months)</td> <td>2.9</td> </tr> </tbody> </table> <p>Safety: The most frequent grade 3 or 4 events were diarrhea and leukopenia. Skin reactions in 89%</p>	Outcome	Percent	ORR (CR+PR) All (N=138) Irinotecan refractory (N=74)	15 12	Median OS (months)	8.4	Median TTP(months)	2.9
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IMCL 0141 ⁴ Phase II Open-label, MC, uncontrolled N=61 Cetuximab 400mg/m ² initial dose then 250mg/m ² weekly	1. EGFR+, irinotecan refractory stage IV colorectal carcinomas 2. PS ≤2	Primary: ORR Secondary: Safety TTP EGFR expression	<table border="1"> <thead> <tr> <th>Outcome</th> <th>Percent (N=57)</th> </tr> </thead> <tbody> <tr> <td>ORR (CR+PR) All Irinotecan refractory</td> <td>9 14</td> </tr> <tr> <td>Median OS (months)</td> <td>6.4</td> </tr> <tr> <td>Median TTP (months)</td> <td>1.4</td> </tr> </tbody> </table> <p>Response did not correlate with intensity of EGFR expression A correlation between the presence and severity of the acne-like rash and survival was observed.</p> <p>Safety: The most frequent grade 3 or 4 events were acne, abdominal pain, asthenia, intestinal obstruction</p>	Outcome	Percent (N=57)	ORR (CR+PR) All Irinotecan refractory	9 14	Median OS (months)	6.4	Median TTP (months)	1.4
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TTP=Time To Progression; NR=non-randomized; MC=multi-center; EGFR=Epidermal Growth Factor Receptor; OS= Overall Survival; ORR=Objective Response Rate (CR+PR)

Other Uses**Squamous cell carcinoma of the head and neck (SCCHN)**

An international, phase III trial by Bonner examined patients with locally advanced SCCHN to determine the impact of combining cetuximab with high dose radiation versus high dose radiation alone on locoregional control of disease.

Outcome	Radiation Alone (N=213)	Radiation + Cetuximab (N=211)
Locoregional Control		
One-year	61%	71%
Two-year	49%	58%
		(p=0.01)
Overall Survival		
Median	28 months	54 months
Two-year	55%	62%
Three-year	44%	57%

Grade 3/4 Clinical Toxicity

Toxicity	Radiation Alone (N=212)	Radiation + Cetuximab (N=208)
Skin Reaction	18%	34%
Hypersensitivity	0	3
Dysphagia	30	25
Nausea/Vomiting	4	2
Fatigue/Malaise	5	4

Phase II Trial in recurrent/metastatic SCCHN refractory to platinum-based therapy

Outcome	Result
Response Rate (PR)	12.6%
Disease Control Rate (PR + SD)	45.6%
TTP	2.3 months
Median Survival (months)	5.9 months

Adverse Effects (Safety Data)⁵

Most common adverse events in combination therapy: acneform rash, leukopenia, asthenia/malaise, diarrhea, nausea, abdominal pain, and vomiting.

Most serious adverse events: Infusion reactions (3%), dermatologic reactions (1%), interstitial lung disease (0.5%), fever (5%), sepsis (3%), kidney failure (2%), pulmonary embolus (1%), dehydration (5%) in patients also receiving irinotecan, diarrhea (6%) in patients also receiving irinotecan.

Incidence of Adverse Events (≥10%) in Metastatic Colorectal Carcinomas

Body system	Cetuximab + irinotecan		Cetuximab Monotherapy	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Whole				
Asthenia	73%	16%	49%	10%
Abdominal pain	45	8	25	7
Fever	34	4	33	0
Pain	23	6	19	5
Infusion reaction	19	3	25	2
Infection	16	1	11	1
Back Pain	16	3	11	3
Headache	14	2	25	3
Digestive				
Diarrhea	72	22	28	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Stomatitis	26	2	11	<1
Dyspepsia	14	0	7	0
Hematologic				
Leukopenia	25	17	1	0
Anemia	16	5	10	4
Metabolic				
Weight loss	21	0	9	1
Peripheral edema	16	1	10	<1
Dehydration	15	6	9	2
Respiratory				
Dyspnea	23	2	20	7
Increased cough	20	0	10	1
Skin				
Acneform rash	88	14	90	10
Alopecia	21	0	5	0
Skin Disorder	15	1	5	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	10	<1
Conjunctivitis	14	1	7	<1
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	9	0

Geriatric Use: 33% of patients in the colorectal trials were greater than 65 years old. No differences in efficacy or toxicity were identified.

Pregnancy Category C: There are no adequate and well-controlled trials of cetuximab in pregnant women, nor have animal reproductive studies been conducted. EGFR is implicated in prenatal development (e.g. organogenesis, proliferation and differentiation in embryo) and human IgG1 does cross the placental barrier, therefore there is potential for cetuximab to be transmitted from a mother to her fetus. All patients

of potential child-bearing years should be counseled on the potential benefits versus risks of cetuximab therapy and pregnancy.

Nursing Mothers: Although human IgG1 is secreted into human breast milk, it is unknown if cetuximab is also secreted. The potential for absorption and harm to an infant is unknown. Because of the long half-life of cetuximab, women should be counseled to discontinue breast feeding during therapy and for 60 days after the last dose of cetuximab.

Precautions/Contraindications

General: Use with caution in patients with hypersensitivity to cetuximab or murine proteins. Patients should wear sunscreen and hats and limit sun exposure during therapy as sun exposure may exacerbate skin reactions.

EGF Receptor Testing: In clinical trials, patients were required to have immunohistochemical evidence of EGFR expression using the DakoCytomation EGFR pharmDx™ test kit. Laboratories proficient in this technology should refer to the DakoCytomation test kit instructions for information on assay performance, tissue fixation, reagents, and procedures.

Immunogenicity: A small number of patients tested positive for non-neutralizing anti-cetuximab antibodies. There does not seem to be a relationship between antibody formation and safety or efficacy, although the timing of sample collection and sensitivity of the antibody assay may affect results.

Infusion Reactions (Black Box Warning): Severe infusion reactions occurred in 3% of patients and were rarely fatal (<1 in 1000). About 90% of reactions occurred during the first infusion. Reactions are characterized by rapid onset of airway obstruction, urticaria, and hypotension and should be treated with standard fluids, epinephrine, corticosteroids, and antihistamines as needed. Severe reactions require immediate interruption of infusion and permanent discontinuation of therapy. Pretreatment with an H1 antagonist (diphenhydramine) is recommended. In clinical trials, mild to moderate infusion reactions were treated by slowing the infusion and continued treatment with antihistamines.

Pulmonary Toxicity: 3 cases of interstitial lung disease and one fatal case of interstitial pneumonitis with non-cardiogenic edema have been reported. Two patients had exacerbation of pre-existing fibrotic lung disease following treatment with cetuximab and irinotecan. An additional case of interstitial pneumonitis was reported in a patient receiving cetuximab plus cisplatin. If there is an acute onset or worsening of pulmonary symptoms interrupt cetuximab therapy and evaluate patient. A diagnosis of ILD warrants permanent discontinuation of cetuximab.

Dermatologic Reactions:^{6,7} Cetuximab produced an acneform rash in 88% of patients, and was grade 3 or 4 in 12%. Complications of the rash include *S. aureus* infections and abscess formation. Patients who develop skin reactions should be monitored for inflammatory and infectious complications and treated appropriately (e.g. topical or oral antibiotics; topical steroids are not recommended). Dose modifications should be instituted for severe acneform rash.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name (cetuximab): rituximab, abciximab, cefotaxime, alemtuzumab, ceftizoxime,
Rituxan, trastuzumab, basiliximab

LA/SA for trade name (Erbix): Rubex, Rituxan

Drug Interactions

There was no evidence of a drug interaction between cetuximab and irinotecan in formal drug interaction studies.

Acquisition Costs

Drug	Dose	Cost/week/patient (\$)	Cost/4 weeks/patient (\$)
Cetuximab Loading Dose	400mg/m ² /2m ² (8 vials)	2,874.32	
Cetuximab Maintenance	250mg/m ² /2m ² /week (5 vials)	1,796.45	7,185.80 (for 16 weeks including LD = 31,617.52)
Irinotecan	125mg/m ² /2m ² /week	1,225.02	4,900.08
Irinotecan	180mg/m ² /2m ² /every 2 weeks	1,662.62	3,3325.24

Cost Analysis

There are no formal economic evaluations of cetuximab therapy in metastatic colorectal cancer at this time. A Budget Impact Model for Managed Care Organizations (MCO's) has been developed and shows the economic impact to be manageable, predictable, and low because the majority of patients in a theoretical MCO are ≤65 years old and are less likely to have a diagnosis of colorectal cancer. This model cannot be applied to the Veteran's Health Administration population.

Conclusions**Clinical Efficacy:**

Cetuximab is a chimeric monoclonal antibody against the epidermal growth factor receptor. EGFR is expressed in over 80% of metastatic colorectal carcinomas. When given in combination with irinotecan as second or third-line therapy in patients who are refractory to irinotecan it produces response rates of 23% (PR's) compared to response rates of 11% when used as monotherapy in the same population. Time to progression was 4.1 months in the combination group and 1.5 months in the monotherapy group. The primary endpoint was tumor response and the planned sample size was not based on a comparison of groups but on an estimation of the response rate to a specified level of precision. While other analyses were presented (time to progression and overall survival) the study was underpowered to detect a clinically meaningful difference.⁸ Response rates, time to progression, and survival were similar in a subpopulation of patients who had also received oxaliplatin-based therapy before progressing on an irinotecan-based therapy. The degree of EGFR expression did not correlate significantly with response rate. Patients who developed a rash had a better response than patients who did not develop a rash.

Safety:

Cetuximab monotherapy is fairly well tolerated. Adverse events in the BOND trial were similar to those in phase I trials and were manageable. Adverse events with combination therapy were heterogeneous and consistent with the known safety profiles of both cetuximab and irinotecan. Infusion reactions may be prevented with the use of pretreatment H1 antagonists and treated with standard therapy and subsequent dose modifications. Skin reactions generally occur within the first three weeks of therapy, may require topical or oral antibiotic treatment for subsequent infections, and may require a dose modification.

Diarrhea and dehydration during combination therapy with irinotecan should be aggressively treated as per recommendations for irinotecan therapy.

Cost: The cost of the addition of cetuximab to irinotecan therapy approximately triples the cost of therapy. When compared to FOLFOX4 therapy as second-line treatment following irinotecan therapy, cetuximab plus irinotecan is approximately two and one-half times the cost of FOLFOX4. As monotherapy following irinotecan failure, cetuximab costs are nearly double that of FOLFOX4 and six times the cost of more conventional therapies with little benefit in terms of response and time to progression.

Recommendations

Place in Therapy: The registration trial showed that cetuximab in combination with irinotecan can resensitize some tumors that are refractory to irinotecan. It was effective for patients as a second and third-line therapy in regard to response rate. However, it was powered for an estimate of response rate, and analyses of time to progression and overall survival are not statistically meaningful because the sample was underpowered for these outcomes. Other clinically useful outcomes (e.g. time to treatment failure and QoL) were not measured but are being evaluated in ongoing trials. Cetuximab monotherapy was approved for use in patients who are intolerant of irinotecan although this is not the population in which it was studied. The clinical usefulness of an 11% response rate and time to progression of 1.5 months with monotherapy is questionable and cannot be readily recommended at this time. Data in head and neck cancers is maturing rapidly and may prove useful in the near future.

In irinotecan refractory disease (when irinotecan is used for first-line therapy of metastatic disease) there is more rigorous outcome data with an oxaliplatin-based regimen as second line therapy. Routine use of cetuximab plus irinotecan as second-line therapy following progression on first-line irinotecan therapy cannot be recommended for all patients at this time with the data that is available. Certainly, there will be patients for whom second-line oxaliplatin therapy is not appropriate due to performance status or pre-existing toxicities; cetuximab plus irinotecan may be considered in these patients. All patients will need to be evaluated for risks and benefits when choosing any second-line therapy. Patients who received oxaliplatin as first-line therapy followed by irinotecan second line who then progress would be candidates for cetuximab plus irinotecan.

Several questions remain about the best use of cetuximab. The issue of whether EGFR expression is predictive of response has not been answered. Some of the specimens tested were from initial surgeries for colorectal cancer and may not represent the tumor at the time of treatment. Also, handling of these earlier specimens was not standardized; degradation of cell surface enzymes may have occurred due to incorrect fixation procedures. The lack of rigorous outcomes for cetuximab monotherapy in this setting raises a question as to the magnitude of any benefit. The lack of QoL and survival data in the combination arm, as well as a lack of comparison to another second-line therapy, makes it difficult to understand the applicability of this regimen. Ongoing trials evaluating QoL, survival, use in first-line therapy, use with FOLFOX4, and adjuvant therapy will help to distinguish which populations will benefit. Ongoing molecular work with EGFR expression and activation will help to further define populations who will gain the most benefit from cetuximab.⁹

Formulary recommendation: At this time, cetuximab should not be added to the national formulary, but should be available to those patients who may receive the most benefit after risks are assessed.

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