



Action Letter

DATE: December 15, 2011

FROM: Helen Chen, MD, Associate Branch Chief, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Bevacizumab (rhuMAb VEGF, NSC 704865)

TO: Investigators for CTEP-supported Studies Involving Bevacizumab (rhuMAb VEGF, NSC 704865)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with bevacizumab, and to request all trials with bevacizumab be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes bevacizumab. See the accompanying list of CTEP trials with bevacizumab.

CTEP believes that with the exception of the addition of ovarian failure, which would affect a subset of patients eligible for bevacizumab trials, the other new and/or modified risk information for bevacizumab in the Comprehensive Adverse Events and Potential Risks (CAEPR) list is very similar to the risk information that is already included in the previous version of the CAEPR and thus would have been communicated to patients in the informed consent document (ICD). Below are CTEP's assessments of the new/modified risks:

- New and/or modified adverse events (AE) terms that are similar to what were already included in the previous CAEPR: (1) Febrile neutropenia is a further specification of the previously identified risk of Neutrophil count decreased, (2) Gastrointestinal obstruction is often a consequence of the previously identified risks of Constipation and Ileus, (3) Osteonecrosis of the jaw is a specific manifestation of the previously identified risks of Infection and Wound dehiscence, and (4) Peripheral sensory neuropathy is an increase in the chemotherapy-rated peripheral neuropathy and therefore only applies to regimens for which neuropathy is already a known risk. When changes such as these are made to the ICD (i.e., changes as to how risk information is presented and/or additional clarifying information and/or small increases/decreases in frequency of risks leading to a new frequency category), it is not necessary to suspend enrollment of new subjects until a revised ICD is reviewed and approved by the Institutional Review Board (IRB).
- The risk of ovarian failure is new. However, this risk is only applicable to female, premenopausal patients and does not pose a risk to the majority of patients that will be eligible for the trials. For this reason, it is not necessary to suspend the entire protocol until IRB approval of the new ICD. The investigators are asked to do the following:

Action Letter

- Accrual will need to be suspended for premenopausal women until a revised ICD is reviewed and approved by the IRB once the final Action Letter is released.
- Accrual of all other patient populations, for which this new event poses no risk, may continue.

In response to the new/modified risk information CTEP is requiring that all trials with bevacizumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on December 29, 2011** or as required based on protocol status (see the General Actions Required Based on Protocol Status section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Helen Chen (helen.chen@nih.gov; 301-496-1196). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since bevacizumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the IRB Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: <http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html>.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised CAEPR (Attachment 1) and ICD risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, AdEERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with bevacizumab.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

Protocol Cover Page: Page Number(s): _____

Version Date: _____

2) Revision of the Protocol CAEPR:

Protocol Section(s) for Insertion of Revised CAEPR (Version 2.2, October 21, 2011): ____

Page Number(s): ____

- The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.
- Added New Risk:
 - Likely: Reproductive system and breast disorders - Other (ovarian failure)
 - Less Likely: Febrile neutropenia; Gastrointestinal obstruction
 - Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Platelet count decreased; Palmar-plantar erythrodysesthesia syndrome
- Increase in Risk Attribution:
 - Changed to Less Likely from Reported But Undetermined: Osteonecrosis of jaw; Peripheral sensory neuropathy
- Decrease in Risk Attribution:
 - Changed to Less Likely from Likely: Diarrhea; Nausea; Vomiting; Fatigue; Headache
 - Changed to Rare But Serious from Less Likely: Acute kidney injury
- Provided Further Clarification:
 - The following footnote was added to Gastrointestinal obstruction: "Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC."
 - The following footnote was added to Osteonecrosis of jaw: "Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates."

Action Letter

- The following footnote was added to Peripheral sensory neuropathy: “Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.”
- The following footnote was added to Reproductive system and breast disorders - Other (ovarian failure): “Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥ 30 mIU/mL) was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level < 30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.”
- Renal and urinary disorders – Other (renal failure) is now reported as part of Acute kidney injury.
- Respiratory, thoracic, and mediastinal disorders – Other (rhinitis) is now reported as Allergic rhinitis.
- Skin and subcutaneous disorders – Other (rash) is now reported as Rash maculo-papular.
- Small intestinal obstruction is now reported as part of Gastrointestinal obstruction.
- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
 - Added: Febrile neutropenia; Colitis; Myalgia
 - Deleted: Myocardial infarction; Intracranial hemorrhage; Ischemia cerebrovascular

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.2, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.1. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.1), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP’s suggested lay terms may change periodically. The risk profile represents CAEPR risks in lay terms in a one-to-one mapping. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the risk profile in any way, please state, “The risk profile has been modified” in the cover memo.

- Added New Risk:
 - Likely: Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown
 - Less Likely: Fever associated with dangerously low levels of a type of white blood cell (neutrophils); Blockage in an organ(s)/part(s) of the digestive tract
- Increase in Risk Attribution:
 - Changed to Less Likely from Reported But Undetermined: Destruction or death of jawbone; Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Decrease in Risk Attribution:
 - Changed to Less Likely from Likely: Diarrhea; Nausea or the urge to vomit; Vomiting; Fatigue or tiredness; Headache or head pain
 - Changed to Rare But Serious from Less Likely: Sudden decrease of kidney function

Action Letter

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to bevacizumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised Bevacizumab CAEPR – Version 2.2, October 21, 2011

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMab VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with *bold* and *italicized* text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, October 21, 2011¹

Adverse Events with Possible Relationship to Bevacizumab (rhuMab VEGF) (CTCAE 4.0 Term)			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<i>Anemia (Gr. 3)</i>
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		<i>Febrile neutropenia (Gr. 3)</i>
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		<i>Supraventricular tachycardia (Gr. 3)</i>
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<i>Abdominal pain (Gr. 3)</i>
	Colitis		<i>Colitis (Gr. 3)</i>
	Constipation		<i>Constipation (Gr. 3)</i>
	Diarrhea		<i>Diarrhea (Gr. 3)</i>
	Dyspepsia		<i>Dyspepsia (Gr. 2)</i>
		Gastrointestinal fistula ²	
	Gastrointestinal hemorrhage ³		<i>Gastrointestinal hemorrhage³ (Gr. 2)</i>
	Gastrointestinal obstruction ⁴		

Action Letter

		Gastrointestinal perforation ⁵	
		Gastrointestinal ulcer ⁶	
	Ileus		
	Mucositis oral		<i>Mucositis oral (Gr. 3)</i>
	Nausea		<i>Nausea (Gr. 3)</i>
	Vomiting		<i>Vomiting (Gr. 3)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		<i>Fatigue (Gr. 3)</i>
	Infusion related reaction		<i>Infusion related reaction (Gr. 2)</i>
	Non-cardiac chest pain		<i>Non-cardiac chest pain (Gr. 3)</i>
	Pain		<i>Pain (Gr. 3)</i>
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		<i>Allergic reaction (Gr. 2)</i>
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection ⁷		<i>Infection⁷ (Gr. 3)</i>
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		<i>Wound dehiscence (Gr. 2)</i>
INVESTIGATIONS			
	Alanine aminotransferase increased		<i>Alanine aminotransferase increased (Gr. 3)</i>
	Alkaline phosphatase increased		<i>Alkaline phosphatase increased (Gr. 3)</i>
	Aspartate aminotransferase increased		<i>Aspartate aminotransferase increased (Gr. 3)</i>
	Blood bilirubin increased		<i>Blood bilirubin increased (Gr. 2)</i>
	Cardiac troponin I increased		
	Neutrophil count decreased		<i>Neutrophil count decreased (Gr. 3)</i>
	Weight loss		<i>Weight loss (Gr. 3)</i>
	White blood cell decreased		<i>White blood cell decreased (Gr. 3)</i>
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		<i>Anorexia (Gr. 3)</i>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		<i>Arthralgia (Gr. 3)</i>
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) ⁸		
	Myalgia		<i>Myalgia (Gr. 3)</i>
	Osteonecrosis of jaw ⁹		
NERVOUS SYSTEM DISORDERS			
	Dizziness		<i>Dizziness (Gr. 2)</i>
	Headache		<i>Headache (Gr. 3)</i>
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy ¹⁰		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	

Action Letter

	Hematuria		<i>Hematuria (Gr. 3)</i>
	Proteinuria		<i>Proteinuria (Gr. 2)</i>
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure) ¹¹			
		Vaginal fistula	
	Vaginal hemorrhage		<i>Vaginal hemorrhage (Gr. 3)</i>
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		<i>Allergic rhinitis (Gr. 3)</i>
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		<i>Cough (Gr. 3)</i>
	Dyspnea		<i>Dyspnea (Gr. 2)</i>
	Epistaxis		<i>Epistaxis (Gr. 3)</i>
	Hoarseness		<i>Hoarseness (Gr. 3)</i>
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		<i>Pruritus (Gr. 2)</i>
	Rash maculo-papular		<i>Rash maculo-papular (Gr. 2)</i>
	Urticaria		<i>Urticaria (Gr. 2)</i>
VASCULAR DISORDERS			
Hypertension			<i>Hypertension (Gr. 3)</i>
	Thromboembolic event		<i>Thromboembolic event (Gr. 3)</i>
		Vascular disorders - Other (arterial thromboembolic event) ¹²	

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

³Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁴Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁵Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

Action Letter

⁶Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁷Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

⁸Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

⁹Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

¹⁰Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

¹¹Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥ 30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level < 30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

¹²Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMab VEGF) trials but with the relationship to Bevacizumab (rhuMab VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation

CARDIAC DISORDERS - Pericardial effusion

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS

HEPATOBIILIARY DISORDERS - Hepatic failure

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)

INVESTIGATIONS - Platelet count decreased

METABOLISM AND NUTRITION DISORDERS - Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis)

NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Seizure

PSYCHIATRIC DISORDERS - Confusion

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

Note: Bevacizumab (rhuMab VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD section(s) for Bevacizumab

Please note that the terminology for CTEP's suggested lay terms may change periodically. The risk profile represents CAEPR risks in lay terms in a one-to-one mapping. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.

Risk Profile for Bevacizumab (CAEPR Version 2.2, October 21, 2011)

Likely:

- Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown
- High blood pressure

Less Likely:

- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Diarrhea
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Blockage in an organ(s)/part(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems

Action Letter

- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Destruction or death of jawbone
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Headache or head pain
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Fainting
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Stuffy or runny nose, sneezing
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Rare But Serious:

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue

Action Letter

- Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- Sudden decrease of kidney function
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For Cooperative Group studies, please follow instructions from Group Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.
2. Accrual of new patients (**premenopausal women only – see instructions on pages 1-2 of this letter**) must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.
3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.
4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of "Active"

- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (<http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf>).
- Suspend accrual of new patients (**premenopausal women only – see instructions on pages 1-2 of this letter**) until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of “Approved”, “Temporarily Closed to Accrual and Treatment”, or “Temporarily Closed to Accrual”

- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of “In Review”

- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of “Closed to Accrual”

If your trial is under a CTEP-held IND:

- Review and follow ALL the instructions outlined in this RRA.
- The information provided in this memo outlines the ONLY changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP’s editorial and administrative update policy (<http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf>).

If your trial is NOT under a CTEP-held IND:

- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow ALL the instructions outlined in this Action Letter. The information provided in this memo outlines the ONLY changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP’s editorial and administrative update policy (<http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf>).
- If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.

E. Trials with a current CTEP status of “Closed to Accrual and Treatment” or “Complete”

- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.