PF-06463922 (Lorlatinib) Named-Patient Early Access

Reference Guide for Physicians

This reference guide provides information on the recommended safety monitoring and dose modifications in case of observed adverse events and the process for safety reporting by physicians who have received approval for compassionate use/named-patient early access of PF-06463922.

1. SAFETY MONITORING

Table 1. Recommended Safety Monitoring

	During PF-06463922 Therapy (1 cycle = 21 days)	After PF-06463922 Therapy
Laboratory Examinations		
Hematology	As clinically indicated	X
Blood Chemistry	As clinically indicated	X
Lipid Profile	Cycle 1: Day 1, Day 14 Cycle 2 and subsequent cycles: Day 1; reduce frequency once lipids stabilize	X
Coagulation	As clinically indicated	
12-lead ECG	As clinically indicated	
Pregnancy Test	If applicable, prior to each cycle	X
Other Clinical Assessments		
Adverse Event and Serious Adverse Event	X	X

Hematology, Blood Chemistry, Lipid Profile, and Coagulation: Suggested tests are listed in Appendix 1 of this reference guide. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed. In patients who develop lipid (cholesterol or triglyceride), hematologic laboratory, coagulation or chemistry laboratory abnormalities, see Dose Modification section.

ECG: If the QTc is prolonged (>500 msec, ie, CTCAE Grade $\geq$ 3), immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of Investigator(s) is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 500 msec the study drug should be held until the QTc interval decreases to < 500 msec. Patients should then re-start the study drug at the next lowest dose level. If the QTc interval has still not decreased to < 500 msec after 2 weeks, or if at any time a patient has a QTc interval > 515 msec or becomes symptomatic, study drug should be discontinued.

Guidance for PR prolongation / AV block is described in Table 7.
Pregnancy Test (for women of childbearing potential only): Pregnancy test should be performed immediately before investigational product administration. Following a negative pregnancy result, appropriate contraception (defined in Life Style Guidelines) must be commenced. Pregnancy tests should also be routinely repeated at every cycle while being treated with PF-06463922, and at the end of PF-06463922 therapy
Adverse Events/Serious Adverse Events: A health care provider (HCP) overseeing the administration of PF-06463922 will identify adverse events that occur in his/her patient throughout the entire period of product administration. Should the HCP participating in this program identify an adverse event (AE) (serious or non-serious), the HCP will provide a full description of the AE or SAE via fax to Pfizer's Drug Safety Unit within 24 hours of HCP awareness.

2. LIFE STYLE GUIDELINES

2.1. Contraception

PF-06463922 is a compound that has a known teratogenic risk associated in animal studies. Two (2) methods of highly effective contraception must be used throughout the study and continued for 90 days after the last dose. The investigator, in consultation with the patient, will select two appropriate methods of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in their consistent and correct use. The investigator, at each study visit, will discuss with the patient the need to use highly effective contraception consistently and correctly and document such conversation in the patient chart. In addition, the investigator will instruct the patient to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception provided the patient remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository). For countries where a spermicide is not available or condom plus

spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy.

2.2. Sunlight Exposure

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity UVb sources such as tanning beds, tanning booths and sunlamps. Patients should be advised to apply sunscreen and wear appropriate clothing to minimize exposure to the sun during treatment with PF-06463922.

2.3. Additional Lifestyle Guidances

Patients will be advised to avoid eating or drinking grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos] that strongly inhibit/induce CYP3A. Because there are no available data on concurrent alcohol use with PF-06463922, patients should be advised to limit alcohol consumption during the study treatment period.

3. DRUG SUPPLY

3.1. Formulation, Packaging and Dosing

PF-06463922 will be supplied for oral administration as 5 mg, 25 mg, and 100 mg acetate solvate tablets or as 25 mg or 50 mg free base tablets in HDPE (High Density Polyethylene) bottles with desiccant. Tablets have different sizes and shapes according to different strengths. Study medication will be supplied by Pfizer. Acetate solvate tablets supplied initially may be followed by free base tablets, which may be of a different strength.

Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

The recommended dose schedule of PF-06463922 is 100 mg taken orally once daily, continuously. Treatment may be continued as long as the patient is deriving clinical benefit from therapy. Administration will be performed on an outpatient basis.

PF-06463922 should be taken with at least 8 oz (240 mL) of water and may be taken with or without food.

Patients should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time. If a patient misses a daily dose, they

must be instructed not to "make it up" the next day. If a patient vomits any time after taking a dose, they must be instructed not to "make it up", but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of PF-06463922. Patients should also be instructed to swallow the medication whole and not chew the tablet prior to swallowing. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

3.2. Recommended PF-06463922 Dose Modifications

Every effort should be made to administer study treatment at the planned dose and schedule.

In the event of significant toxicity, dosing may be withheld and/or reduced as described in the tables below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Dose modifications of an oral medication given continuously may occur in two ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle; this may persist, delaying the start of a new cycle.
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

3.2.1. Dosing Interruptions

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in the dose modification Tables 3 to 7 below.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle.

3.2.2. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-06463922 dose may need to be reduced when treatment is resumed.

Table 2. PF 06463922 Dose Reductions

Current Dose Level	Dose Level -1	Dose Level -2	Dose Level -3
100 mg QD	75 mg QD	50 mg QD	25 mg QD

In cases where no specific dose adjustments for Grade 1 or Grade 2 treatment-related toxicity are provided, investigators should always manage their patients according to their medical judgment which may include dose reduction or interruption based on the particular clinical circumstances.

Patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation should be at investigator discretion for appropriate patient management.

3.2.3. Dose Modifications for PF-06463922-Related Toxicities

For reference, the following guidance may be instructive:

Table 3. Non-Hematologic Toxicities

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
Pancreatitis	If both amylase and lipase are Grade ≤ 2 in the absence of radiological findings of pancreatitis: continue at the same dose level without dosing interruption. Repeat lipase and amylase. If radiologically confirmed pancreatitis: withhold dose. Repeat radiology and lipase and amylase weekly. If appropriate, resume treatment at one dose level lower if radiology has returned to baseline and lipase and amylase are Grade ≤ 2.		Discontinue	Discontinue
Pneumonitis (in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Asymptomatic, radiographic findings only: No need for dose adjustment. Initiate appropriate monitoring. Symptomatic: Withold current dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume treatment at the same dose. Discontinue permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment.	Withold current dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume treatment at one dose level lower. Discontinue permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment.	Discontinue	Discontinue
Prolonged QTc interval	Assess electrolytes and concomitant medications	Assess electrolytes and concomitant medications	Withhold dose Assess electrolytes	Discontinue

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
	Correct any electrolyte abnormalities, or hypoxia Continue at the same dose level	Correct any electrolyte abnormalities, or hypoxia Continue at the same dose level	and concomitant medications Correct any electrolyte abnormalities, or hypoxia. Upon recovery to Grade ≤1 resume treatment at one dose level lower.	
LVEF Dysfunction	Not Applicable	Not Applicable	Discontinue	Discontinue
Other (see separate tables below for Lipid and CNS toxicities and subsection on PR Interval Prolongation below)	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤ 1 (or has returned to baseline), then reduce the dose by 1 level or rechallenge at the same dose *.	Withhold dose until toxicity is Grade ≤ 1(or has returned to baseline), then reduce the dose by 1 level*. Or discontinue at the discretion of the investigator.

* Patients who develop asymptomatic Grade 4 hyperuricemia or Grade 3 hypophosphatemia may continue PF-06463922 without dose modification at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require PF-06463922 dose modification.

** In cases where no specific dose adjustments for Grade 1 or Grade 2 treatment-related toxicity are provided, investigators should always manage their patients according to their medical judgment which may include dose reduction or interruption based on the particular clinical circumstances.

Table 4. Hematologic Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Lymphopenia	Continue at the same dose level.	Continue at the same dose level.	If no evidence of infection or other clinically significant toxicity, continue at the same dose; otherwise, withhold dose until toxicity is Grade ≤ 1 (or baseline) then rechallenge at the same dose or reduce the dose by 1 dose level	If no evidence of infection or other clinically significant toxicity, continue at same dose; otherwise, withhold dose until toxicity is Grade ≤ 1 (or baseline), then rechallenge at the same dose or reduce the dose by 1 dose level
Other	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤ 1 (or has returned to baseline), then rechallenge at the same dose or reduce the dose by 1 dose level.	Withhold dose until toxicity is Grade ≤ 1 (or has returned to baseline) then rechallenge at the same dose or reduce the dose by 1 dose level.

Table 5. Lipid Elevation Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Total Cholesterol	Continue at the same dose. Consider introducing use of a statin or other lipid lowering agent as appropriate based on investigator's medical judgment.	Introduce the use of a statin or other lipid lowering agent as appropriate, and continue at the same dose.	Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent, or change to a new agent. Either continue study drug at the same dose without interruption or withhold dose until toxicity is Grade ≤ 2 and then continue at the same dose.	Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/ lipid lowering agent, or change to a new agent. Withhold dose until toxicity is Grade ≤ 2 and then reduce the dose by 1 dose level or rechallenge at the same dose.
Triglycerides	Continue at the same dose. Consider introducing use of a statin or other lipid lowering agent as appropriate based on investigator's medical judgment.	Introduce the use of a statin or other lipid lowering agent as appropriate, and continue at the same dose.	Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent or change to a new agent. Either continue study drug at the same dose without interruption or withhold dose until toxicity is Grade ≤ 2 and then continue at the same dose.	Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent or change to a new agent. Withhold dose until toxicity is Grade ≤ 2 and then reduce the dose by 1 dose level or rechallenge at the same dose.

Table 6. CNS Effect Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
CNS effects*	Continue at the same dose or withhold dose until recovery to baseline and then continue at the same dose	Continue at same dose or withhold dose until recovery to Grade ≤ 1. Consider dose reduction or rechallenge at the same dose.	Withhold dose until toxicity is Grade ≤ 1. Reduce dose to the next lower dose.	Discontinue

* Examples of CNS effects could include changes in speech, memory, sleep, cognition, or vision

PR Interval Prolongation

PR-interval prolongation has been observed in patients receiving PF-06463922. Below are guidelines for patients who develop first-degree, second-degree, or complete heart block. Guidelines distinguish between asymptomatic vs. symptomatic heart block. Symptoms that could be attributed to heart block include, but are not limited to include, dizziness, lightheadedness, and fatigue, shortness of breath, fainting and palpitations.

If a patient develops second-degree or third-degree heart block, discussion with the sponsor is warranted to discuss appropriate management.

Table 7. Atrioventricular Block

Event	Asymptomatic	Symptomatic
First-degree heart block (PR-interval >200 msec)	**No dose hold or reduction needed.** Assess concomitant medications. Monitor closely by obtaining pre-dose ECG at next visit, even if unscheduled. Instruct patient to call if symptoms develop that may be related to heart block.	**Withhold dose**. Assess concomitant medications. Obtain ECG in approximately 48 hours and re-assess symptoms and PR-interval. Restart at same dose or consider dose reduction when symptoms resolve.

Second-degree heart block	**Withhold dose.** Assess concomitant medications. Repeat ECG in approximately 48 hours. Instruct patient to call if symptoms develop that may be related to heart block. Restart at same dose or consider dose reduction if subsequent ECG does not show 2nd degree block.	**Withhold dose.** Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic heart block persists. Resume at reduced dose only when symptoms resolve AND 2nd degree block resolves. If patients revert to 1st degree block with no symptoms, resume at reduced dose.
Complete Heart Block	**Withhold dose**. Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with heart block. If heart block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, may resume at full dose. If no pacemaker placed, restart at reduced dose only when symptoms resolve AND PR < 200 msec.	

Additionally, for patients with PR interval prolongation, the concomitant use of medicinal products known to prolong PR interval is not advised and these should be used with caution

3.3. Concomitant Medications

PF-06463922 can potentially alter the pharmacokinetics of coadministered drugs that are eliminated by the CYP pathways. In vitro, PF-06463922 induces CYP2B6, inhibits CYP2C9 and inhibits P-glycoprotein (P-gp). Although in vitro, PF-06463922 has shown time-dependent inhibition of CYP3A4/5, in vivo PF-06463922 has been preliminarily shown to induce CYP3A4.

Some of these same pathways that PF-06463922 inhibits/induces are those which metabolize PF-06463922 (CYP3A4, CYP2C19 and CYP2C8). The net effect including auto induction is currently under investigation. Thus, the following cautions are provided:

- PF-06463922 metabolism may be inhibited by strong/moderate CYP3A4 leading to a potential increase in PF-06463922 toxicities. Therefore, strong/moderate inhibitors are not permitted from 10 days prior to the first dose of PF-06463922 until study treatment discontinuation (*Strong CYP3A4 Inhibitors e.g.:* grapefruit juice or grapefruit/grapefruit

related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, nefazodone, lopinavir, troleandomycin, mibefradil, conivaptan; *Moderate CYP3A4 inhibitors e.g.:* Erythromycin, verapamil, atazanavir, fluconazole, darunavir, diltiazem, delavirdine, aprepitant, imatinib, tofisopam, ciprofloxacin, cimetidine).

- PF 06463922 metabolism may be induced when taking strong CYP3A4 inducers (eg, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St. John's Wort) resulting in reduced plasma concentrations. Therefore, coadministration of PF 06463922 in combination with these and other strong CYP3A4 inducers is not recommended from 12 days prior to the first dose of PF 06463922 until study treatment discontinuation

- PF-06463922 inhibits CYP2C9 (in vitro), so concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices, such as warfarin, phenytoin or celecoxib, may have increased effect. Concomitant use of a CYP2C9 substrate is not permitted, or caution is warranted

- PF-06463922 induces CYP2B6 (in vitro) so concurrent use of drugs that are CYP2B6 substrates, such as bupropion and efavirenz, may have less effect. Concomitant use of a CYP2B6 substrate is not permitted or caution is warranted

- PF-06463922 induces CYP3A4 (in vivo) so concurrent use of drugs which are CYP3A4 substrates may have less effect. Therefore, PF-06463922 coadministration with a CYP3A4 substrate of a narrow therapeutic index, such as astemizole, terfenadine, cisapride, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, (alfentanil and fentanyl, including transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine) is not permitted, or caution is warranted

- PF-06463922 inhibits P-gp (in vitro) so concurrent use of drugs which are P-gp substrates with a narrow therapeutic index may have increased effect. Therefore, PF-06463922 coadministration with P-gp substrates with a narrow therapeutic index, such as digoxin, or quinidine are not permitted, or caution is warranted

3.3.1. Other Anti-Tumor or Experimental Drugs

No additional systemic anti-tumor therapy is recommended while patients are receiving a study therapy. Additionally, the concurrent use of select herbal supplements is not recommended.

Bisphosphonate therapy for metastatic bone disease is permitted.

Palliative radiotherapy on study is permitted but, in view of the current lack of data about the interaction of PF-06463922 with radiotherapy, PF-06463922 treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment after recovery from acute radiation toxicities to baseline.

3.3.2. Proton-pump Inhibitors

A study to assess the impact of PF-06463922 coadministration with proton-pump inhibitiors (PPIs) (eg, lansoprazole [Prevacid®], rabeprazole [Aciphex®], pantoprazole [Protonix®], and esomeprazole [Nexium®]) has been conducted. After review of the study results, the observed effect of PPIs on PF-06463922 exposure was minor, and not clinically significant. As a result, there is no restriction on the use of PPIs (or H_2-antagonists, or locally-acting antacids) used concomitantly with PF-0646922. Further details of this study can be found in the Investigator Drug Brochure.

3.3.3. Testosterone Replacement

Testosterone replacement therapy is only recommended in the presence of signs and symptoms clearly attributable to hypogonadism in consultation with an endocrinologist, who should also exclude any potential confounding effects of elevated prolactin and/or estradiol, or a significant recent change in corticosteroid dose, before doing so.

3.3.4. Lipid-Lowering Therapy

Treatment with a statin is recommended at the first signs of elevated (Grade 1) cholesterol and/or triglycerides. Clinically, PF-06463922 has limited data, but it is a moderate inducer of CYP3A4. Combined with the in vitro data that PF-06463922 can itself be metabolized by CYP3A4, 2C19, 2C8 and UGT1A4 as well as inhibit 2C9 and induce 2B6, the choice and dose of statin should be considered carefully.

Statins can be metabolized or inhibited by the same CYP450 pathways as PF-06463922 (Table 8). Therefore, the statins with the least involvement of the CYP450 enzyme systems to use concomitantly with PF-06463922 would be pitavastatin or pravastatin followed by rosuvastatin. However, clinical drug-drug interactions have not been formally studied with PF-06463922, so careful monitoring is advised.

Similarly, if hypertriglyceridemia requires treatment, the drugs with the least involvement of the CYP450 enzyme systems to use concomitantly with PF-06463922 would be fenofibrate or fish oils followed by nicotinic acid (Table 9). Again, clinical drug-drug interactions have not been formally studied with PF-06463922, so careful monitoring is advised.

Table 8. Pharmacokinetic Properties of Statins

Generic name (or equivalent)	***Pitavastatin***	***Pravastatin***	***Rosuvastatin***	***Atorvastatin***	***Simvastatin***	***Lovastatin***	***Fluvastatin***
Metabolism†	++	+	+	+++	+++	+++	+++
Metabolizing CYP enzymes (of lactone or acid form)	(2C9)	(3A4)	2C9 (2C19)	3A4 (2C8)	3A4 2C8	3A4 2C8?	2C9
Inhibitor of CYP3A4‡			+	+	+	+	+
Inhibitor of CYP2C9‡			(+)				+
Triglyceride lowering effect	22-30%**	11-14%*	17%*	14-19%*	10-14%*	13%*	0-5%***

Parentheses indicate minor significance.

†Three plus signs indicate extensively metabolized, and 1 plus sign indicates limited metabolism, eliminated mainly unchanged.

‡A plus sign indicates yes, and a minus sign indicates no.

* Baseline TG 100-200 mg/dL; Effect of Statins vs Placebo on Triglyceride Levels in 10 Primary and Secondary Placebo-Controlled Outcome Trials. http://www.medscape.org/viewarticle/589010
** Baseline TG ≥ 150 mg/dL; Cardiovascular Drug Reviews. 2003; 21(3): 199–215.
*** Am J Cardiol 2004;93:31–39

adapted from Clin Pharmacol Ther 2006;80:565-81

Table 9. Pharmacokinetic Properties of Lipid Lowering Agents

		Fibric Acids		***Fish Oils***
Generic Name (or equivalent)	***Nicotinic Acid***	***Gemfibrozil***	***Fenofibrate***	***Ethyl esters of omega-3 fatty acids***
Metabolism‡	-	-	-	-
Metabolizing CYP enzymes (of lactone or acid form) ‡	-	-	-	-
Inhibitor of CYP3A4‡	-	-	-	-

Inhibitor of CYP2C9‡	-	+++	++	-
Inhibitor of CYP2C19‡	-	++	+	-
Inhibitor of CYP1A2‡	-	+	-	-
Triglyceride lowering effect (TG ≥ 150 mg/dL)	20-50%*	20-50%*	36% - 55%[a]	45%[a]
Drug Interactions	Caution should be used when prescribing niacin with statins	Concomitant administration with statins is contraindicated	May increase exposure to pravastatin and its metabolite (13-29%) when used concomitantly	
‡A plus sign indicates yes, and a minus sign indicates no. [a] primary hypertriglyceridemia – severe hypertriglyceridemia (Baseline TG levels >500 mg/dL)				
* NCEP-ATP III, 2001.				

3.3.5. Surgery

Caution is advised on theoretical grounds for any surgical procedures. The appropriate interval of time between surgery and PF-06463922 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06463922 is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate PF-06463922 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

4. ADVERSE EVENT REPORTING

An HCP overseeing the administration of PF-06463922 will identify adverse events that occur in his/her patient throughout the entire product administration. Should the HCP participating in this program identify an adverse event (AE) (serious or non-serious) the HCP will provide a full description of the AE via fax to Pfizer's Drug Safety Unit within 24 hours of HCP awareness.

Reference definitions for reporting period, adverse event, serious adverse event, severity, exposure during pregnancy and adverse event assessment can be found in Appendix 2 of this treatment guideline.

If the adverse event is fatal or life-threatening, notification to Pfizer should be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded adverse event reports as well as to the initial and follow-up reporting of Exposure during pregnancy and

Exposure during breast-feeding cases. In the rare event that the HCP does not become aware of the occurrence of an adverse event immediately (eg, if an outpatient patient initially seeks treatment elsewhere), the HCP is to report the adverse event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all adverse events, the HCP is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an HCP may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information may be quite detailed and in general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the adverse event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer's Drug Safety Unit.

5. REPORTING REQUIREMENTS TO REGULATORY AUTHORITIES

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

APPENDICES

1. Suggested Safety Laboratory Tests

Hematology Panel		Blood Chemistry Panel		Lipid Panel		Coagulation
1	Hemoglobin	1	ALT	1	Total Cholesterol	PT or INR
2	Platelets	2	AST	2	LDL	PTT
3	WBC	3	Alkaline Phosphatase	3	HDL	
4	Absolute Neutrophils	4	Sodium	4	Triglycerides	
		5	Potassium			
		6	Total Calcium			
		7	Total Bilirubin			
		8	BUN or Urea			
		9	Serum Creatinine			
		10	Albumin			
		11	Lipase			
		12	Amylase			

2. Reference Definitions for Reporting Period, Adverse Event, Serious Adverse Event, Severity, Exposure During Pregnancy, and Adverse Reaction Assessment

Reporting Period

Adverse events (serious and non-serious, regardless of causality) are reported to Pfizer's Drug Safety Unit (DSU) from the time the patient has taken the first dose of treatment through and including 28 calendar days after last dose of administration. Please refer to the Pfizer Compassionate Use/Named Patient Agreement letter for the local contact information for your country.

If the malignancy has a fatal outcome during treatment or within 28 calendar days post the last dose of treatment, then the event leading to death must be reported to Pfizer's DSU.

Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage.

Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breast-feeding;
- Medication error;

- Occupational Exposure

Worsening of signs and symptoms of the malignancy under study should be reported as AEs. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

Medication Errors

Medication errors may result from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength. Medication errors are reportable irrespective of the presence of an associated AE/SAE.

Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in drug dosing or discontinuation from drug, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the HCP or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious Adverse Events

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

- Progression of the malignancy (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during PF-06463922 administration or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see Section on Severity Assessment).
- Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in the emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.
- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
- For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

Concurrent with:

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥3 times the upper limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment, and the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Hospitalization

AEs reported from studies associated with hospitalization or prolongation of hospitalization, are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

Severity Assessment

As required on the adverse event case report forms, the HCP will report adverse event events using concise medical terminology (verbatim) and use the following definition of severity in accordance with the Common Terminology Criteria (CTC) term for Adverse Events (Version 4.0, http://ctep.cancer.gov/reporting/ctc.html) to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

Causality Assessment

The HCP's assessment of causality must be provided for all AEs (serious and non-serious); the HCP must record the causal relationship, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An HCP's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the HCP does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the HCP's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the HCP determines an SAE is associated with study procedures, the HCP must record this causal relationship in the source documents, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the HCP must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the HCP must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The HCP will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the

event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the HCP should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the HCP assesses the neonatal death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the HCP. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the HCP will provide the study patient with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The HCP must document on the EIU Form that the patient was given this letter to provide to his partner.

Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE Report form is maintained in the study master file.