Cancer Therapy: Clinical
See commentary p. 4305

Clinical Cancer Research

Inconsistent Labeling of Food Effect for Oral Agents across Therapeutic Areas: Differences between Oncology and Non-Oncology Products

Soonmo Peter Kang[1,2] and Mark J. Ratain[1,2,3]

Abstract

Purpose: Several recent oral oncology drugs were labeled for administration in fasted states despite the fact that food increases their bioavailability. Because this was inconsistent with the principles of oral drug delivery, we hypothesized that there were inconsistencies across therapeutic areas.

Experimental Design: Oral agents approved by the U.S. Food and Drug Administration from January 2000 to May 2009 were included in our study. Comparison of the food labeling patterns between oncology and non-oncology drugs was made using Fisher's exact test.

Results: Of the 99 drugs evaluated, 34 showed significant food effects on bioavailability. When food markedly enhanced bioavailability, eight out of nine non-oncology drugs were labeled "fed" to take advantage of the food-drug interaction, whereas all oncology drugs (n = 3) were labeled to be administered in "fasted" states (Fisher's exact test, P = 0.01).

Conclusions: Drug labeling patterns with respect to food-drug interactions observed with oncology drugs are in contradiction with fundamental pharmacologic principles, as exemplified in the labeling of non-oncology drugs. *Clin Cancer Res; 16(17); 4446–51. ©2010 AACR.*

Many new antineoplastic agents are intended for daily administration requiring the availability of oral formulations. Oral therapies could improve a patient's quality of life by offering convenience and a sense of control, as well as avoiding the cost of administering parenteral agents (1, 2). However, oral cancer drugs could present special challenges. With increased patient responsibility, nonadherence to potent agents is a major concern to oncologists (3). In addition, oral agents generally have more complex pharmacokinetic challenges compared with drugs administered intravenously.

Administration of oral drugs with meals could influence drug absorption and systemic exposure. The food effect on oral bioavailability is the result of a complex interplay of drug, formulation, intestinal physiology, and meals. As food could either increase or decrease bioavailability, the interaction should be studied early in drug development to provide rational dosing recommendations for the pivotal clinical trials (4).

Questions were raised in the recent past regarding the labeling of lapatinib, a dual tyrosine kinase inhibitor used to treat advanced breast cancer (5). Lapatinib is labeled to be taken fasting, despite the fact that food markedly improved the bioavailability of the drug, exemplifying a missed opportunity to take advantage of pharmacologically favorable food-drug interactions (6). We hypothesized that there might be a systematic difference between oncology and non-oncology products in terms of food labeling. The present work examines the food labeling patterns of oncology and non-oncology drugs to highlight the inconsistency across the therapeutic areas and to suggest potential implications.

Materials and Methods

The present study is based on the examination of all new molecular entities (NME) that were approved for oral administration by the U.S. Food and Drug Administration (FDA) between January 2000 and May 2009. The primary source of data was the FDA web site (http://www.accessdata.fda.gov/scripts/cder/drugsatfda). This included both clinical pharmacology/biopharmaceutics reviews and labels. A search of published literature was conducted in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) to gather missing information from the FDA web site (7–19). Main search terms used were food effect, bioavailability, pharmacokinetics, and the agents' names.

Data captured for the purpose of the present analysis included drug approval date, drug name, therapeutic area, magnitude of food effect, interindividual variability (IIV)

Authors' Affiliations: [1]Department of Medicine, [2]Committee on Clinical Pharmacology and Pharmacogenomics, and [3]Cancer Research Center, University of Chicago, Chicago, Illinois

Corresponding Author: Mark J. Ratain, Section of Hematology/Oncology, Department of Medicine, The University of Chicago, 5841 South Maryland Avenue MC 2115, Chicago, IL 60637. Phone: 773-702-4400; Fax: 773-702-3969; E-mail: mratain@medicine.bsd.uchicago.edu.

doi: 10.1158/1078-0432.CCR-10-0663

Translational Relevance

Knowledge of food-drug interactions is critical in optimizing the delivery of oral anticancer agents. We found a systematic difference between oncology and non-oncology drugs in how food-drug interactions are applied in their labels. When food enhanced bioavailability, non-oncology drugs were labeled "fed" to take advantage of the food-drug interaction, whereas oncology drugs were labeled to be administered in "fasted" states. These oncology drug labeling decisions are in contradiction with fundamental pharmacologic principles as exemplified in non-oncology drugs; therefore, they might lead to suboptimal dosing strategies and outcomes. Although there is understandable urgency that might be unique to oncology, it is important that regulatory agencies insist on uniform application of principles of clinical pharmacology in oncology drug development.

of area under the curve (AUC) of fed and fasted states, dosing recommendation with regards to meals (fed, fasted, or either), and black box safety warnings in drug labels.

We included all NMEs with food effect bioavailability study results available on the FDA web site or via publication, and divided them into two categories (oncology versus non-oncology) based on their indications and divisions of the U.S. FDA involved in the approval processes. We used AUC as the reflection of the extent of drug exposure, and used the ratio of fed to fasted AUC to measure the food effect. In keeping with guidance from the FDA, food effect was determined to be significant if the AUC ratio (fed/fasted) was >1.25 or <0.8 (20). We then subclassified NMEs with a ratio >1.5 and <0.5, a magnitude of food effects that will likely have clinical implications. A comparison of food effects was made between oncology and non-oncology drugs that met these criteria.

The dosing recommendations regarding meal intakes (fasted, fed, or either) available in the dosage and administration section of package inserts were surveyed to study how food effect results are applied. Comparison of the drug label patterns between oncology and non-oncology drugs with marked food effects were made by using Fisher's exact test.

To assess the effect of food intake on IIV of AUC, we compared coefficients of variation (CV) of AUC between fasted and fed states of 23 drugs with significant food effects and available PK data. Black box safety warnings were available from package inserts and the frequency of black box warnings were compared between oncology and non-oncology drugs. We also surveyed package inserts of NMEs

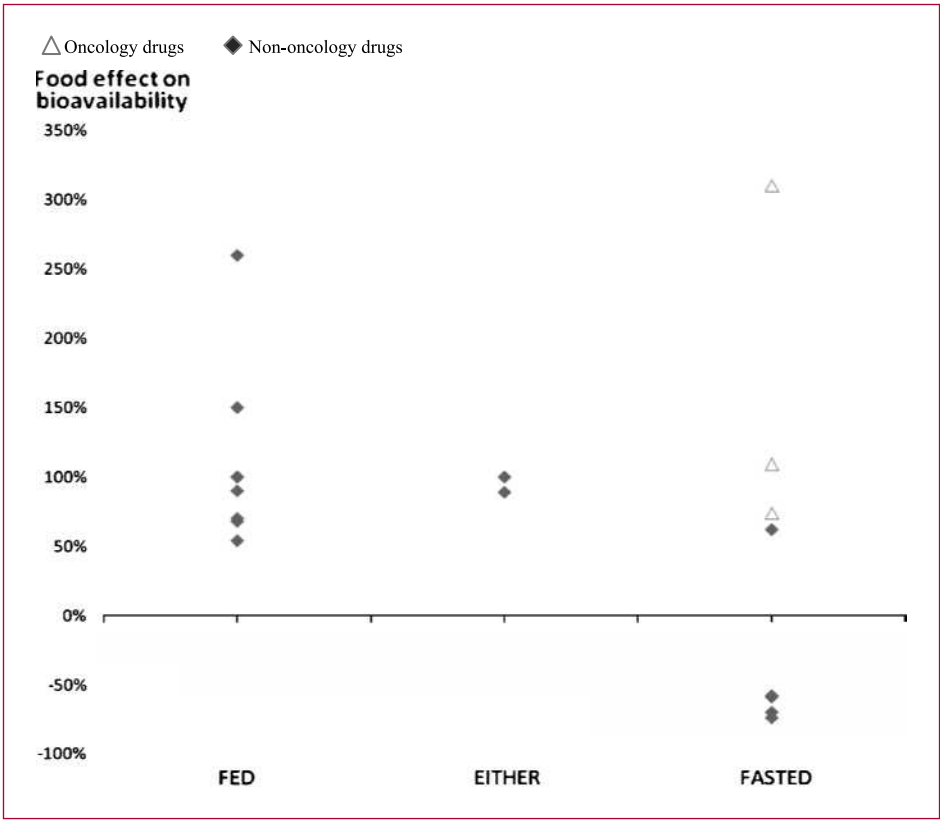

Fig. 1. Application of marked food effects on labels: oncology versus non-oncology. Food recommendations on 18 drugs with marked food effects (AUC ratio ≥1.5 or ≤0.5). *Y*-axis represents change of AUC from fasted states to fed states. Food recommendations in labels were to be administered with meals (fed), without meals (fasted), or without regards to meals (either). When food recommendations were made either fed or fasted on drugs with marked increase of AUC, oncology drugs were labeled as fed whereas most non-oncology drugs were labeled fed (Fisher's exact test, $P = 0.01$).

Table 1. Summary of food effects and labels of 23 NMEs that were approved by the FDA from January 2000 to May 2009

Name	AUC ratio (fed/fasted)	CV fasted	CV fed	CV fed-CV fasted	Label
Lapatinib	4.1	68%	52%	–16%	Fasted
Posaconazole	3.6	36%	41%	5%	Fed
Erlotinib	2.09	36%	18%	–18%	Fasted
Alfuzosin HCl	2	69%	40%	–29%	Fed
Ziprasidone HCl	2	44%	22%	–22%	Fed
Nitazoxanide	1.9	35%	37%	2%	Fed
Rifaximin	1.89	51%	26%	–25%	Either
Nilotinib	1.74	35%	30%	–5%	Fasted
Cinacalcet	1.68	60%	46%	–14%	Fed
Deferasirox	1.62	36%	31%	–5%	Fasted
Etravirine	1.54	111%	80%	–31%	Fed
Vorinostat	1.38	43%	32%	–11%	Fed
Rufinamide	1.34	30%	28%	–2%	Fed
Gefitinib	1.33	55%	40%	–15%	Either
Darunavir	1.3	15-35%	15-35%	0%	Fed
Tapentadol	1.26	36%	29%	–7%	Either
Rasagiline	0.8	30%	32%	2%	Either
Voriconazole	0.76	125%	150%	25%	Fasted
Sorafenib	0.69	36%	53%	17%	Fasted
Sodium oxybate	0.65	38%	42%	4%	Fasted
Tegaserod maleate	0.42	26%	32%	6%	Fasted
Eltrombopag	0.41	28%	27%	–1%	Fasted
Aliskiren	0.3	49%	60%	11%	Fasted

NOTE: NMEs with both AUC and CV data available were included.

with black box warnings to identify warnings related to food intake and associated risks.

Results

We identified 104 oral NMEs that were approved by the FDA between January 2000 and May 2009. This included 11 oncology drugs and 93 non-oncology drugs. Most of these NMEs (n = 99) had food effect study results reported in the clinical pharmacology section of the package inserts.

Influence of meals on drug exposure

Of 99 NMEs with available food effect study results, about one-third (n = 34) showed significant food effects on their bioavailability. Marked food effects were observed in nearly 20% of drugs (14 increasing and 4 decreasing AUC). Of the 18 NMEs with marked food effects, 3 were oncology agents and 15 were non-oncology agents.

Application of food effect study to drug labeling

The vast majority (94%, n = 93) of NMEs had specific recommendations with respect to food coadministration: 60% (n = 56) without regard to meals, 24% (n = 22) to be administered with food, and 16% (n = 15) to be administered in the fasted state. Only six NMEs had no specific recommendations regarding food intake.

Analysis of 14 NMEs with marked increase in AUC with food revealed that there are different food labeling patterns between oncology and non-oncology drugs. For the non-oncology drugs, the marked increase in bioavailability with food generally (with one exception) led to recommendations to administer drugs in a fed state to take advantage of the favorable food effects. The opposite labeling pattern was observed for oncology drugs, as all three drugs with a marked increase in bioavailability with food were recommended to be administered in fasting states (Fig. 1).

Food significantly decreased (by ≥20%) the bioavailability of 11 NMEs, and the majority were labeled to be administered in fasted state (7 fasted, 1 fed, and 3 either). Sorafenib was the only oncology NME in this group, which is labeled to be taken fasting. Four NMEs showed a marked decrease of bioavailability (by ≥50%) with food, and all of them were labeled to be administered in a fasted state to maximize their bioavailability (Fig. 1).

Influence of meals on IIV of AUC

Of 34 NMEs with significant food effects, 23 had CV data available through the FDA web site (package insert or Clinical Pharmacology and Biopharmaceutics Review)

or via publications (Table 1). In general, we observed an inverse relationship between food effects on bioavailability and IIV. In most cases, increase of bioavailability with food resulted in a decrease of IIV of AUC (Fig. 2). Of 16 drugs with a significant increase of bioavailability with meals (and with available CV data), only one drug (posaconazole) showed an increase of bioavailability associated with a slight increase of IIV; the CV increase with food was merely 5%. The CVs of three oncology drugs with marked positive food effects were decreased by food intake, which indicate that coadministration of drugs with food did not add to the risk of unpredictable exposure, but in fact improved the exposure variability probably as a result of enhanced bioavailability. On the other hand, when food had a negative effect on a drug's bioavailability, administering the drug with food resulted in greater IIV compared with administering it without food (Fig. 2).

Safety warning label

We surveyed NMEs with a black box safety warning to determine whether marked food-drug interactions are incorporated in such a warning. The frequencies of black box warnings were similar between oncology and nononcology drugs (36% versus 32%). Of three drugs with marked food-drug interactions, only one NME (nilotinib) had its food effect on drug exposure clearly described in the black box safety warning. Lapatinib, which showed the greatest food effect on its AUC, did not have a black box warning regarding its food-drug interaction, even though QT prolongation is an acknowledged risk (Table 2).

Discussion

Dosing strategies to enhance bioavailability offer several advantages to delivery of oral drugs. They include reduced gastrointestinal toxicity (from unabsorbed drugs) and decreased intraindividual and/or IIV in drug exposure (4, 21). Increased drug absorption also reduces wasted drug product and improves pharmacoeconomic efficiency.

Unwarranted food restrictions might compromise the practicality of drug administration for patients and result in decreased adherence. The complexity of the drug regimen is a major reason for nonadherence, and interventions such as reminder systems have been shown to improve adherence (3, 22–26). Daily routines such as breakfast, could serve as great reminders to take medications consistently. Hence, a dosing schedule tied to routine meals will be easier for patients (particularly elderly cancer patients taking multiple oral medications) and can be a great way to improve adherence, which is recognized as a serious challenge in cancer treatments with oral agents.

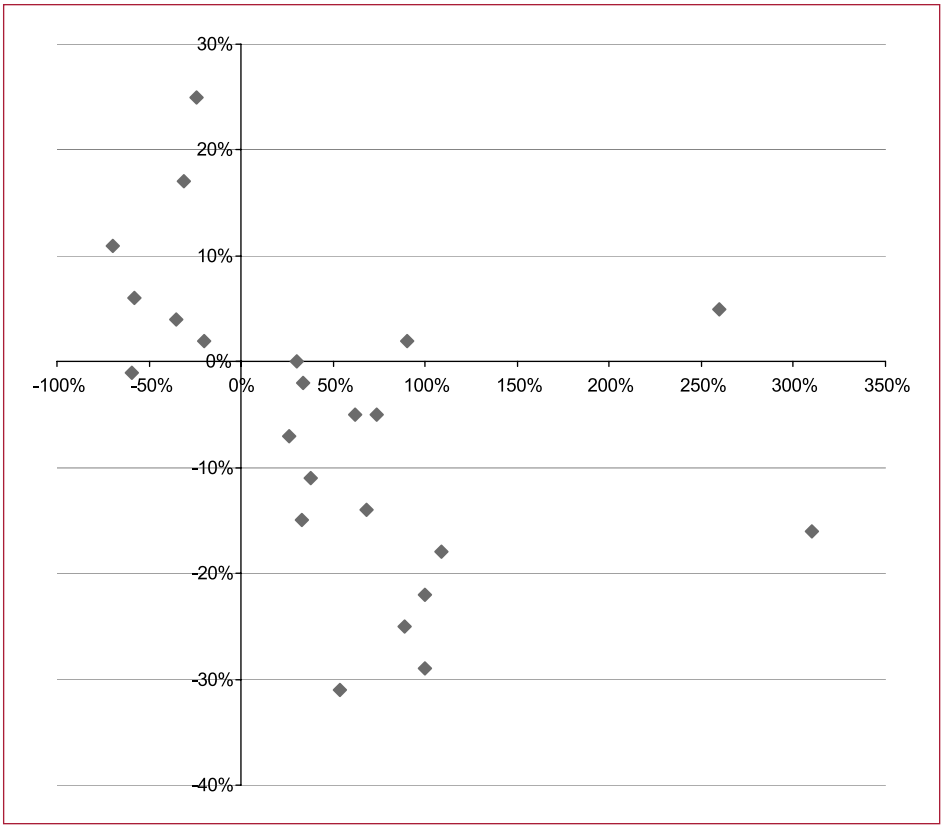

Fig. 2. Relationship between food effects on bioavailability and interindividual variation of drug exposure. *Y*-axis represents change in coefficient of variance of AUC from fasted to fed states. *X*-axis represents food effect on mean AUC. Examination of 23 drugs with significant food effects and available CV data revealed an inverse relationship between change in BA and change in IIV of drug exposure from prandial states.

Table 2. Drugs with positive food effect with meals and black box safety warnings

Drugs with positive food effects* and black box safety warnings	Therapeutic area	Black box warning	Risk of QT prolongation	AUC ratio (fed/fasted)	Warning regarding food effect	Label
Ziprasidone HCl	Non-oncology	Elderly with dementia related psychosis with increased risk of death	Yes	2	No	Fed
Lapatinib	Oncology	Hepatotoxicity	Yes	4.1	No	Fasted
Nilotinib	Oncology	QT prolongation	Yes	1.74	Yes	Fasted

*Positive food effect: increase of AUC by at least 25% with meals.

The food labeling pattern of recently approved oral oncology drug products is inconsistent with fundamental principles of oral drug delivery. The labels of three agents (erlotinib, nilotinib, and lapatinib) minimized bioavailability through food restrictions, which is in contrast to the labeling principles used for all other classes of oral agents. In the absence of a scientific basis for food restrictions, one can hypothesize that the atypical food labeling pattern of some oral oncology drug products might be a consequence of external pressures (corporate and regulatory pressures) in an era of immense competition in oncology. Phase II (and occasionally registration) studies are often initiated prior to the completion of an appropriate food-effect study (14, 27). Because the default position seems to be fasting, this has occasionally resulted in the completion of all clinical studies with a fasting dosing regimen in the absence of adequate supportive pharmacokinetic data (14, 27, 28). Furthermore, there is little interest from the industry in conducting such studies later if the result would be a lower labeled dose because this would result in reduced revenues, unless accompanied by an increase in pricing. Thus, regulators should require such studies after approval, if the prior studies have not adequately addressed this issue.

A food effect study conducted in a timely fashion could facilitate pharmacologically rational drug dosing strategies. The optimal time for studying food-drug interactions would be at the end of the first phase I clinical trial: once the dose-toxicity relationship has been identified. At the very minimum, the appropriate prandial state(s) should be determined before undertaking pivotal trials, given the importance of such trials in drug labeling.

It should also be noted that food restriction in the first phase I clinical trial, before the characterization of food effects, is not ideal from standpoints of pharmacology and patient safety. Because a marked decrease of AUC with food is uncommon, it is probably most appropriate—in the absence of data—to begin studies of NMEs in a fed state. On the other hand, nearly 15% of recently approved NMEs showed a marked increase in bioavailability with food. Starting the first phase I trials in fed conditions will reduce the risks of severe adverse events due to inadvertent food-drug interactions.

We recognize the limitation of this retrospective analysis, particularly with regard to identifying the rationale for apparently irrational decisions given the complex nature of oncology drug development processes and decision-making. There are potential limitations in comparing drug labels of oncology and non-oncology drugs due to different potencies, indications, and targeted patients. The inability to study other factors relevant for food labeling, such as the comparison of IIV of drug exposures between prandial states with differing food contents, due to the lack of such data, is another limitation of this report. Despite these limitations, our analysis clearly illustrates a distinct food labeling pattern with oncology products that is inconsistent with the fundamental principles routinely practiced in other disciplines. Although there is understandable urgency that might be unique to oncology, it is important that regulatory agencies insist on the uniform application of principles of clinical pharmacology, regardless of the effect on the sponsor's timelines.

Disclosure of Potential Conflicts of Interest

M.J. Ratain: commercial research grant, Bristol-Myers Squibb; other commercial support (as meeting organizer, including funding under negotiation), Abbott, Amgen, Astellas, AstraZeneca, Bayer, Biogen Idec, Bristol-Myers Squibb, Eli Lilly, Genentech, Johnson & Johnson, Merck, Novartis, Sanofi Aventis, Takeda; patents pending, sorafenib for pulmonary hypertension and EGFR diagnostics; consultant/advisory board, Abbott, Ambit, Astellas, AstraZeneca, Baxter, Cyclacel, Genentech, Hoffman-La Roche, MGI Pharma, Mylan, Onyx, OSI Pharmaceuticals, Novartis, Pfizer, Schering-Plough, Takeda, Teva; S.P. Kang: employment, Merck (effective July 2010).

Grant Support

S.P. Kang was supported by Clinical Therapeutics T32 GM007019 from NIH.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 03/16/2010; revised 04/22/2010; accepted 04/23/2010; published OnlineFirst 08/24/2010.

References

1. Parsad SD, Ratain MJ. Prescribing oral chemotherapy. BMJ 2007; 334:76.
2. DeMario MD, Ratain MJ. Oral chemotherapy: rationale and future directions. J Clin Oncol 1998;16:2557–67.
3. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. J Natl Cancer Inst 2002;94: 652–61.
4. Singh BN, Malhotra BK. Effects of food on the clinical pharmacokinetics of anticancer agents: underlying mechanisms and implications for oral chemotherapy. Clin Pharmacokinet 2004;43:1127–56.
5. Ratain MJ, Cohen EE. The value meal: how to save $1,700 per month or more on lapatinib. J Clin Oncol 2007;25:3397–8.
6. GlaxoSmithKline: TYKERB label http://usgskcom/products/assets/us_tykerbpdf2007.
7. Williams DD, Peng B, Bailey CK, et al. Effects of food and antacids on the pharmacokinetics of eltrombopag in healthy adult subjects: two single-dose, open-label, randomized-sequence, crossover studies. Clin Ther 2009;31:764–76.
8. Scholler-Gyure M, Boffito M, Pozniak AL, et al. Effects of different meal compositions and fasted state on the oral bioavailability of etravirine. Pharmacotherapy 2008;28:1215–22.
9. Polinsky RJ. Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. Clin Ther 1998;20:634–47.
10. Koch KM, Reddy NJ, Cohen RB, et al. Effects of food on the relative bioavailability of lapatinib in cancer patients. J Clin Oncol 2009;27: 1191–6.
11. Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother 2003;47:2788–95.
12. Sekar V, Kestens D, Spinosa-Guzman S, et al. The effect of different meal types on the pharmacokinetics of darunavir (TMC114)/ritonavir in HIV-negative healthy volunteers. J Clin Pharmacol 2007;47:479–84.
13. Padhi D, Salfi M, Harris RZ. The pharmacokinetics of cinacalcet are unaffected following consumption of high- and low-fat meals. Am J Ther 2007;14:235–40.
14. Ling J, Fettner S, Lum BL, Riek M, Rakhit A. Effect of food on the pharmacokinetics of erlotinib, an orally active epidermal growth factor receptor tyrosine-kinase inhibitor, in healthy individuals. Anticancer Drugs 2008;19:209–16.
15. Purkins L, Wood N, Kleinermans D, Greenhalgh K, Nichols D. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. Br J Clin Pharmacol 2003;56 Suppl 1:17–23.
16. Rubin EH, Agrawal NG, Friedman EJ, et al. A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancer. Clin Cancer Res 2006;12:7039–45.
17. Galanello R, Piga A, Cappellini MD, et al. Effect of food, type of food, and time of food intake on deferasirox bioavailability: recommendations for an optimal deferasirox administration regimen. J Clin Pharmacol 2008;48:428–35.
18. Cardot JM, Lecaillon JB, Czendlik C, Godbillon J. The influence of food on the disposition of the antiepileptic rufinamide in healthy volunteers. Biopharm Drug Dispos 1998;19:259–62.
19. Zhou H, Khalilieh S, Lau H, et al. Effect of meal timing not critical for the pharmacokinetics of tegaserod (HTF 919). J Clin Pharmacol 1999;39:911–9.
20. Services USDoHaH. Guidance for industry: food-effect bioavailability and fed bioequivalence studies. Food and Drug Administration Center for Drug Evaluation and Research (CDER); 2002.
21. Hellriegel ET, Bjornsson TD, Hauck WW. Interpatient variability in bioavailability is related to the extent of absorption: implications for bioavailability and bioequivalence studies. Clin Pharmacol Ther 1996;60:601–7.
22. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin 2009;59:56–66.
23. Ruddy KJ, Partridge AH. Adherence with adjuvant hormonal therapy for breast cancer. Ann Oncol 2009;20:401–2.
24. Stone VE, Hogan JW, Schuman P, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the her study. J Acquir Immune Defic Syndr 2001;28:124–31.
25. Stone VE. Strategies for optimizing adherence to highly active antiretroviral therapy: lessons from research and clinical practice. Clin Infect Dis 2001;33:865–72.
26. Walsh JC, Horne R, Dalton M, Burgess AP, Gazzard BG. Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. AIDS Care 2001;13:709–20.
27. Reigner B, Verweij J, Dirix L, et al. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. Clin Cancer Res 1998;4:941–8.
28. Novartis. Tasigna® (nilotinib) capsules package insert. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022068lbl.pdf.