GEORGETOWN UNIVERSITY MEDICAL CENTER

Center for Drug Development Science

Departments of Pharmacology and Medicine

June 20, 2001

Dockets Management Branch (HFA-305),
Docket No. 00N-1269
Food and Drug Administration,
5630 Fishers Lane, rm 1061
Rockville, MD 20857

Re: IMPORTANCE OF INCLUSION OF INFORMATION CONCERNING NON-COMPLIANCE WITH THE LABEL-RECOMMENDED DRUG REGIMEN. Docket No. 00N-1269, RIN 0910-AA94. Comments on Proposed Rule "Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels".

Dear Sir or Madam:

INTRODUCTION

The Center for Drug Development Science (CDDS), Georgetown University, Washington DC, an academic center that advances drug development sciences through its research, educational and technical assistance programs, recognizes the FDA approved drug label as the single most important collection of drug knowledge available to guide prescribers and patients in safe and effective drug therapy. FDA's proposed changes in the drug labeling requirements (highlights section, index, reorganization, and certain content revisions) are all strongly supported by CDDS.

RECOMMENDATIONS

CDDS wishes to call your attention to the importance of requiring critical information concerning full compliance or deviations from full compliance with the label-recommended drug regimen. Specifically, CDDS recommends the following for your consideration:

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1. Requirement for a mandatory section in all labels concerning "advice when the label-recommended therapeutic regimen is fully complied".
2. Inclusion in this mandatory section of "advice when the label-recommended therapeutic regimen is interrupted".
3. Inclusion in this mandatory section of "advice on what to expect upon resumption of dosing".
4. Inclusion in this mandatory section of "advice on how to resume therapy".
5. In the absence of adequate information to inform 1- 4 above, a mandatory statement "efficacy and safety under conditions of complete compliance or missed doses has not been studied".

Our recommendation for a mandatory label section including "advice when the label-recommended therapeutic regimen is fully complied", is motivated by recognition that label statements describing expectations of degree of effectiveness and safety are ordinarily derived from analyzing phase 3 clinical trials using the FDA mandated intention-to-treat (ITT) approach (ICH Guidance on Statistical Principles for Clinical Trials, 1998). This approach, which requires inclusion of data from all randomized patients regardless of deviations from the trial protocol (including incomplete compliance with the drug regimen), yields an underestimate of the average level of beneficial and adverse outcomes, alike. Thus, an individual patient who fully complies with the recommended drug regimen may experience a higher level of benefit or adverse effects compared with the average effect estimated using the ITT approach.

Our recommendation for a mandatory label section including "advice when the label-recommended therapeutic regimen is interrupted" is motivated by recognition that missed doses or multi-dose lapses may lead to diminished efficacy, or adverse consequences associated with pharmacologic reactions due to withdrawal of established exposure to the medication.

Our recommendation for a mandatory label section including "what to expect upon resumption of dosing" following interruption of the recommended regimen is motivated by recognition that adverse reactions due to exaggerated "first dose" effects can recur when full maintenance doses are resumed after lapses of dosing.

Our recommendation for "advice on how to resume therapy" is motivated to provide safe resumption of effective therapy.

BACKGROUND

Definitions

The definition of patient compliance (which some call adherence) is "the extent to which the patient's dosing history corresponds to the prescribed regimen of drug administration" (1). As is well-documented in the literature, errors of omission predominate in ambulatory pharmacotherapy,(1-6) with the result that there are many instances in which the interval between doses is substantially longer than called-for by the recommended regimen. During these longer-than-prescribed intervals, drug actions wane, leaving the patient deprived of the therapeutic actions of the prescribed drug. The rate at which drug actions wane, however, is not

only drug-specific, but product-specific, given that different formulations of the same drug may have very different kinetics and dynamics (7,8).

Model Labeling

The model for compliance-informed labeling is that provided by the low-dose, combined estrogen-progestin oral contraceptives. The label has two sections, one of which conveys the general information about how contraceptive effectiveness depends upon punctual remedication, the other of which gives specific details of what the patient should do, upon recognizing that the forthcoming dose has been delayed, or that one or more scheduled dosing times have passed without the corresponding doses having been taken. The key language in each section follows:

Under the heading "Contraceptive effectiveness", the following is written: "Oral contraceptives or 'birth-control pills' are used to prevent pregnancy and are more effective than other non-surgical methods... The chance of becoming pregnant is less than 1% ... when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle."

Under the heading "What to do if you miss pills", the following is written:

"If you miss 1 active pill, take it as soon as you remember. You do not need to use a back-up birth control if you have sex."

"If you miss 2 active pills in a row in weeks 1 or 2, take 2 pills on the day you remember and 2 pills the next day. You may become pregnant if you have sex in the 7 days after you miss pills. You MUST use another birth control method ... for those 7 days."

"If you miss 2 active pills in a row in the 3rd week, THROW OUT the rest of the pill pack and start a new pack that same day... You MUST use another birth control method for [the next] 7 days." ...

The importance of these recommendations lies in the fact that they address two basic informational needs of prescribers and patients. First, they provide evidence-based information on the limits of deviation from the prescribed regimen that are consistent with full effectiveness of the product. Second, they provide the patient with evidence-based information on how best to phase back into correct dosing, with least risk of the consequences of a period of ineffective drug action ... in this instance, breakthrough ovulation and the risk of conception.

The provision of explicit instructions for phasing back to correct dosing is helpful, to avoid the situation where a patient, upon realizing at, e.g., 3AM, that the previous morning's dose has been missed, takes the missed pill and then feels compelled to use 3AM as the time for each subsequent daily pill, based on the perceived need for 24 hour intervals between doses.

The experimental basis for these recommendations are the results of a series of studies in which interdose intervals have been experimentally prolonged, coincident with serial measures of plasma levels of pituitary luteinizing hormone, to detect the ovulating surge of that hormone – the signal that breakthrough ovulation has occurred (9-13). In like manner, drugs of various other classes have been studied by a similar protocol, e.g.,

Antihypertensives (14-17)
Antidepressants (18)

These studies show a wide variation between products of the same drug class in the need for punctuality in remedication. For example, in the above cited study of antidepressant drugs of the SSRI category, fluoxetine is much more 'forgiving' of delayed remedication than sertraline or paroxetine, and in the study by Johnson and Whelton (14), betaxolol was capable of maintaining antihypertensive activity out to the 48th hour since the last-taken dose, in contrast to atenolol, which could do so only to about the 30th hour.

"Forgiveness"

The concept of 'forgiveness' has an explicit definition: "the post-dose duration of therapeutically effective drug action minus the prescribed interval between doses" (1). In the case of the low-dose combined oral contraceptives, the post-dose duration of therapeutically effective drug action, inferred from the labeling, is 48 hours and the prescribed interval is 24 hours, giving a forgiveness of 24 hours. For atenolol, based on the data of Johnson and Whelton (14), the post-dose duration of therapeutically effective drug action is 30 hours, and the prescribed interval between doses is 24 hours, giving a forgiveness of 6 hours. The data of Rosenbaum, et al. indicate major differences in forgiveness among the three antidepressant drugs tested (18). The importance of the forgiveness concept is that it can help guide prescribers and patients toward the use of more, rather than less, forgiving products when there is evidence that the patient is not capable of punctually maintaining a dosing schedule.

Non-compliance in HIV Therapy

For ethical reasons, not all agents can be studied in the manner of the above-described, controlled manner, e.g., antiretroviral drugs. In such situations, reliance must be placed on observational data, e.g. (4,6). It is noteworthy that the presently available protease inhibitors appear to require punctual remedication both to assure full antiretroviral action, with reduction of viral loads, and also to prevent emergence of drug-resistant human immunodeficiency virus (4,19).

Recently Prof. Joel Gallant of Johns Hopkins made the following statement in respect to the situation with antiretroviral treatment: "Now that antiretroviral therapy is so effective, adherence has never been a more important issue. To derive the full benefit from their therapy, patients must fully understand the benefits of treatment and the risks associated with nonadherence. Outpatient care settings must develop a comprehensive and consistent plan for supporting and evaluating patient adherence." (20) Such 'comprehensive and consistent plans' should be based on best-available, explicit information how commonly occurring lapses in dosing, which are well-documented to occur during antiretroviral drug treatment, impact the effectiveness of antiretroviral treatment, and how best to phase back to correct dosing when such lapses occur.

Need for Labeling Information on Non-compliance

We recognize evidence sufficient to provide such labeling information is presently available for few products. That pragmatic fact does not obviate the need for such information. We suggest that the labeling headings, "[drug action] Effectiveness Depends upon Correct Dosing" and "What to do if you miss [dosage form}s" be made part of every prescription drug indicated for multiple-dose administration, giving the manufacturer the option to make the statement that no information is available at this time.

Further aspects of this topic are the exceptional drug effects that occur during multi-day lapses in dosing, e.g., 'rebound' effects upon sudden cessation of dosing and recurrent 'first-dose' effects when dosing resumes. The hazard of rebound effects with beta aderenergic receptor antagonists of the non-sympathomimetic class (e.g., propranolol, atenolol, metoprolol, and others) is well documented (21-24), but mainly conceived of as a matter for the prescriber to consider when a regimen change is called for, rather than as a matter for patients to be concerned about when they happen to miss sequential doses. Likewise, in the case of peripheral vasodilators and other drugs that require a careful, initial titration of dose from an initially low dose – the so-called 'first-dose effect' drugs – there is a need to warn patients who happen to miss sequential doses that, for safety reasons, they should not immediately resume full-strength dosing, but should consult their physician for phase-in dosing instructions. That recommendation, of course, implies the need for explicit instructions to prescribers on the best sequence to follow for phase-in dosing. Present labeling information includes statements such as "If [product] administration is discontinued for several days, therapy should be restarted using the initial dosing regimen" -- from the labeling for doxazosin. The presence of this information in the "Dosage and Administration" section implies that the instruction applies for physician-initiated interruptions in dosing, as might occur when a patient undergoes general anesthesia and surgery, but does not carry the message to patients, whose predilection to multiday lapses in dosing is well-documented.

To summarize our views, we feel that compliance-informed labeling is an essential part of full-disclosure, with the following aims:

- to encourage proper compliance with recommended dosage regimens,
- to provide information on the degree of precision that a patient must maintain in remedication, in order to prevent loss of therapeutic drug action
- to help patients minimize the adverse consequences of diminished or absent effectiveness during periods of delayed or omitted doses
- to help patients avoid hazardous rebound or recurrent first-dose effects during and after multi-day lapses in dosing
- to help prescribers select more forgiving, rather than less forgiving, medicines for patients who are prone to occasional lapses in dosing.

Thus, there are both efficacy and safety dimensions of compliance-informed labeling.

Looking back at the groundbreaking process by which the oral contraceptives acquired compliance-informed labeling, one sees that the impetus came, not from manufacturers, but from foundations and academic groups interested in the improvement of family planning. The cooperation of the Agency with this effort, the experimental basis for which began to be defined as early as 1979, led finally to adoption of compliance-informed labeling in the early 1990's. While the result is clearly a model for all chronic-use medicines, the process for attaining this therapeutic objective ought to be regularized and facilitated. That objective can be met by adopting the policy that all medicines having recommended regimens which involve sequential doses include headings that are suitable paraphrases of those used in the oral contraceptive labeling: "[product] Effectiveness Depends upon Correct Dosing" and "What to do if you miss [dosage forms]". The fact that most products will have empty sections under these headings should encourage, rather than discourage, this change. If, as seems to be increasingly the case, patients and physicians want this information, it will facilitate the competitive standing of

products that have such information over those that do not, with gradual filling-in of the blanks in this important aspect of ambulatory pharmacotherapy.

Some of these points were presented by one of us (JU) during his CASE Lecture at FDA on February 27, 2001.

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