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February 7, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: *Docket No. 99D - 5047*

Name of Document: Guidance for Industry: Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

Dear Sir or Madam:

Reference is made to the December 7, 1999 Federal Register notice announcing the availability of a Guidance for Industry: Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

AstraZeneca has reviewed this guidance and our comments are attached.

Thank you for your consideration.

Sincerely,

Elizabeth Fenna
Senior Regulatory Project Manager
Regulatory Affairs

99D-5047

CS

Guidance for Industry Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

General comments:

- We believe the guidance should provide recommendations indicating at what phase during the drug development the different categories of studies should be performed. Recommendations for particular types of drugs would also be helpful.
- Defining and characterizing hepatic impairment, unlike renal impairment, can be less than precise. While the guidance recommends Child-Pugh, there is a body of opinion (see for example the attached paper by members of the Swedish MPA in Clin. Pharmacol. Ther. 1999, 66, 201) which suggests that the Child-Pugh scoring can be a very poor predictor of drug metabolizing capacity. In the area of cancer drugs where impairment may be due to metastases rather than cirrhosis, we believe alternative approaches may be better (see for example the attached work of the Glasgow group in Cancer Chemother. Pharmacol., 1998, 42, 229). Thus, while more flexibility in ways of assessing hepatic impairment are allowed in the guidance (we are very comfortable with section VB), some areas of the guidance imply that the use of Child-Pugh is the only recommended method.
- There does not seem to be enough emphasis on the situation where metabolic activation is *required* for activity, i.e., for pro-drugs or compounds where a significant proportion of the activity is due to active metabolites. While this is mentioned in several places, we recommend that this information be provided in a separate section.
- Due to secondary effects of the disease in patients with hepatic impairment there is a potential for change in PD but *not* in PK of drugs, e.g. drugs with CNS depressant effects or anti-coagulants. This fact could be discussed more in the document.
- The route of administration of a drug may have an influence on whether a study in hepatic impairment is relevant, such as for drugs which barely reach the systemic circulation, e.g. those with local action on the skin with poor absorption. This could be added under IIIB page 3, with the heading 'When Studies May Not Be Important'.

- We recommend that age, sex and body-weight matched healthy volunteers be used as controls as opposed to actual patients with the disease under study as recommended in this guidance. PK and/or PD results in patients with the disease under study with normal liver function may be confounded by that disease and/or a co-medication.
- Determination of absolute bioavailability, i.e. to study PK after both oral and intravenous dosing, could be recommended for drugs with extensive pre-systemic elimination intended for oral dosing. This is important for both drugs with (e.g. pro-drugs) and without active metabolite(s).
- With regard to active metabolites, a general recommendation of when they should be analyzed and evaluated, i.e., what is a significant contribution to the pharmacological effect would be helpful. Here again a prodrug is a special case to be mentioned.
- We recommend that guidance be provided on the formulations to be used in the study and any related concerns.
- The use of correlation coefficients between Child-Pugh scores and oral clearance is dubious. The independent variable is categorical, with a large spacing between the mildest hepatic status (C-P = 5) and controls (C-P = 0 presumably). This makes the estimate of the correlation coefficient likely to be biased, particularly in small samples. In addition, the selection of patients to ensure a wide range of C-P scores means that the correlation coefficient is likely to be over-estimated: conversely, in the reduced design, the correlation coefficient is likely to be under-estimated due to the restricted range of C-P scores. Finally, if there is a non-linear or polynomial relationship between C-P and PK, what value is the correlation coefficient? There are better ways of estimating this. Again, popularity does not imply usefulness. We believe that the use of correlation coefficients may not be the optimal approach.

Specific comments

Section/page number	Comment
Page 3, 1st paragraph III A. "When Studies May Be Important"	Some clarification on what is meant by "substantial portion" would be useful (we suggest >33%). In both this case and the 20% for those with narrow therapeutic ranges, a further useful clarification would be to state that 1) these proportions refer to humans and 2) they refer to that fraction of the drug which is absorbed (also relevant under IIIB).

<p>Page 4 IV A. Reduced Study Design 1. Study Participants</p>	<p>We propose that the reasons for choosing the Child-Pugh classification should be discussed separately and not under the heading of reduced study design.</p> <p>Directly under the heading (the subheading 1. Study Participants) we recommend that it be stated what kind of labeling this design is aimed at (mild and moderate impairment). See the text following the heading B. Basic Full Study Design on top of page 6.</p> <p>With regard to polymorph metabolic enzymes, a more standard nomenclature is CYP2D6 and CYP2C19. Furthermore, if polymorph enzymes have a major contribution in the metabolism, the study needs to be performed in extensive metabolizers since this should give a better indication of change in clearance in patients with compromised hepatic function.</p> <p>A good way of assessing the overall metabolic capacity of the liver would be to study the activity of several different metabolic enzymes using a cocktail approach containing several model substrates. Furthermore, a relationship between liver function and PK would optimally be made between oral clearance of the study drug and the clearance of the model compound which is metabolized by the same isozyme as the study drug.</p>
<p>Page 5 2. Drug Administration</p>	<p>A finding of linear PK in healthy subjects cannot exclude nonlinear behavior in hepatic impairment, thus a steady state design is the optimal choice.</p>
<p>Page 8 C. Development of Dosing Recommendations</p>	<p>An additional clarification in the section that describes how to demonstrate that a dose adjustment is unnecessary would be appreciated. Using a strict "bioequivalence" approach would be simplest but it may be unrealistic for a drug with any significant degree of hepatic metabolism. This is where the population PK approach becomes very helpful. However, in reality the experience is that it is quite difficult to get these hepatically impaired patients (especially the Child-Pugh class B and C) into clinical trials thus making it very difficult to properly interpret the data from the small number of hepatically impaired patients who do enrol.</p> <p>If dose adjustment is "necessary", what is the goal of this adjustment, to give a dose that will result in a similar</p>

C_{max} as a non-impaired patient or to give the same AUC (i.e. exposure) as in the non-impaired patient? If so, what is the implication in terms of need to develop multiple dosage strengths?

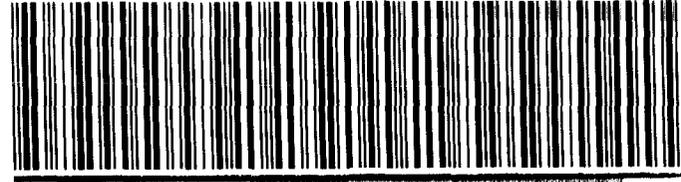
Clarification on distinction between "no effect" (i.e. same as bioequivalent) and "no need to adjust dose" (i.e. <2-fold difference) would be useful and the impact on the labeling would be useful.

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