DECISION

No. 5/29.02.2008

on approval of the Guideline on the evaluation of pharmacokinetics of medicinal products in patients with impaired hepatic function

The Scientific Council of the National Medicines Agency, set up based on Minister of Public Health Order No. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 29.02.2008, in accord with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as further amended, agrees on the following

DECISION

Single article - The Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function is approved, according to the Annexes which are integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on the evaluation of pharmacokinetics of medicinal products in patients with impaired hepatic function

CHAPTER I
General provisions

Art. 1. – This Guideline is a translation and adaptation into Romanian of the EMEA CPMP/EWP/2339/02 Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function and should be interpreted in accordance with provisions of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, along with all the other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

a) Pharmacokinetic Studies in Man *(Notice to Applicants*, Vol. 3C, 3CC3A, 1987)

b) The Investigation of Drug Interactions (CPMP/EWP/560/95)

c) Validation of Analytical Procedures (ICH topic Q2A and Q2B)

d) Structure and Content of Clinical Study Reports (ICH topic E3)

e) Good Clinical Practice (ICH topic E6)

f) General Considerations for Clinical Trials (ICH topic E8)

Art. 2. - (1) This Guideline is intended to assist applicants during development of medicinal products.

(2) Provisions included in this Guideline are only meant for guidance; any deviations from their content should be explained and discussed in the Expert reports/Clinical Overview.

CHAPTER 2
Introduction

Art. 3. - (1) Pharmacokinetic studies are used to identify special subgroups of patients in whom an alternative dosing regimen may be indicated for efficacy and/or safety reasons.

(2) Since liver is an important organ with respect to drug disposition, patients with hepatic impairment constitute an important subgroup of such special populations.

Art. 4. - (1) Hepatic function decreases with age, but due to the high capacity of the liver this is considered not to change the pharmacokinetics to a clinically relevant extent.

(2) Liver disease, however, is known to be a common cause of altered pharmacokinetics of drugs. Hepatic function can be decreased through different pathophysiological mechanisms.

(3) Worldwide, chronic infections with hepatitis B or C are the most common causes of chronic liver disease, whereas in the western world, chronic and excessive alcohol ingestion is one of the major causes of liver disease.

(4) Other causes are uncommon diseases such as primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune chronic active hepatitis.

(5) Ongoing destruction of the liver parenchyma in chronic liver diseases ultimately leads to liver cirrhosis and the development of portal hypertension; however, even if liver cirrhosis is established, the residual metabolic function of the liver may be rather well preserved for many years because of regeneration of hepatocytes.

(6) Clinical symptoms related to hepato-cellular failure and portal hypertensions are most importantly ascites, oesophageal varices and encephalopathy.

(7) Serum markers of liver failure are low serum albumin and a prothrombin deficiency.

(8) Serum bilirubin as well as other liver tests may or may not be affected to a varying degree, e.g. depending on the liver disease (cholestatic versus hepatocellular).

(9) Liver cirrhosis is irreversible in nature, but progression can be modified by e.g. abstinence of alcohol in alcohol liver cirrhosis.

Art. 5. - (1) The pharmacokinetics and pharmacodynamics of medicinal products may be altered by liver disease through different mechanisms; the effects most often depend on the severity of hepatic impairment.

(2) The effects on pharmacokinetics can be difficult to predict due to consequences of shunting of blood past the liver (both porto-systemic and intra-hepatic), impaired hepatocellular function, impaired biliary excretion and decreased protein binding.

(3) Factors that influence the need for pharmacokinetic data in patients with hepatic impairment, and interpretation of these data, are the intended use of the drug, pharmacokinetic characteristic features in otherwise healthy individuals and pharmacokinetic/pharmacodynamic relationships (PK/PD). Based on this, the major concern (side effects or lack of efficacy) should be identified.

Art. 6. - (1) No obvious marker exists for characterising hepatic function with respect to prediction of drug elimination capacity, in contrast to renal impairment.

(2) Therefore, dose recommendations may not be as accurate for hepatic impairment as they can be for renal impairment.

(3) Therefore, one of the primary aims of studies in patients with hepatic impairment might be to identify patients at risk.

Art. 7. - It is the objective of this guideline to make recommendations regarding:

a) In what situations studies of pharmacokinetics should be performed in subjects with impaired hepatic function;

b) The design of pharmacokinetic studies in subjects with impaired hepatic function;

c) Data presentation, analysis, and evaluation of results;

d) Reflection of these results in the Summary of product Characteristics (SPC) in terms of dosing schemes, contraindications, special precautions and warnings for use and description of pharmacokinetic properties.

Art. 8. - (1) It should be emphasised that due to the complex influence of liver disease on the pharmacokinetics of medicinal products and the lack of specific markers, the aim of this guideline is to stimulate further research rather than to provide specific recommendations.

(2) More knowledge is needed within this area and the regulatory requirements must be developed in parallel with the scientific progress.

CHAPTER III
When to perform pharmacokinetic studies in patients with impaired hepatic function

Art. 9. - Pharmacokinetic studies in subjects with impaired hepatic function are recommended in the following situations:

a) The medicinal product is likely to be used in patients with impaired hepatic function and

b) Hepatic impairment is likely to significantly alter the pharmacokinetics (especially metabolism and biliary excretion) of the medicinal product and/or its active metabolites and

c) A posology adjustment may be needed for such patients taking into account the PK/PD relationship.

Art. 10. - (1) The lack of any study in patients with hepatic impairment should be accompanied by a justification.

(2) Lack of data may be justified if the drug is not intended to be used in patients with hepatic impairment.

(3) If the medicinal product is likely to be used in these patients, the applicant should discuss the potential for hepatic impairment to influence the pharmacokinetics (of parent medicinal product, active and "inactive" metabolites) and should include relevant information in the SPC (see also section IV).

(4) Lack of data may lead to restriction in the use of the medicinal product (not only warnings but also contraindications).

CHAPTER IV
Study design

Art. 11. - (1) The primary goal of a study in patients/subjects with impaired hepatic function is to identify patients at risk in terms of severity of hepatic dysfunction.

(2) Depending on the extent to which the pharmacokinetic parameters are affected, the next major objective is to determine the extent to which the dosage should be adjusted to reduce the risk of under or over treatment in these patients.

Art. 12. - (1) When designing a pharmacokinetic study, the normal pharmacokinetic properties of the medicinal product should be the starting point.

(2) Taking elimination characteristics into account, the sponsor should consider which type(s) of hepatic conditions are likely to affect the pharmacokinetics and should focus on including subjects with abnormalities in relevant markers.

IV.1. Classification of hepatic impairment

Art. 13. - (1) There are several systems that aim to categorise the severity of hepatic impairment.

(2) Presently, no well-established, adequate markers for hepatic function in terms of drug elimination capacity are available.

The Child-Pugh classification

Art. 14. - (1) The Child-Pugh classification is the most widely used and is one way of categorizing hepatic function; however, it was not developed for the purpose of predicting drug elimination capacity.

(2) Using this classification, the subjects are grouped on the basis of two clinical features (encephalopathy and ascites) and three laboratory-based parameters (S-albumin, S-bilirubin and prothrombin time).

(3) Hepatic dysfunction is categorised into groups called A, B and C or “Mild”, “Moderate” and “Severe” corresponding to 5-6, 7-9 and 10-15 scores, respectively (See Annex).

(4) As a result, even subjects with a normal hepatic function are given a total score of 5 points (since each variable gives a score of 1 point even within the normal range) and would consequently be classified as having mild hepatic impairment.

Art. 15. - (1) With regard to the clinical chemistry parameters, i.e. S-albumin, S-bilirubin and prothrombin time, none of these is specific for liver disease only.

(2) Albumin is low due to decreased synthesis by the hepatocytes in chronic liver disease but may also be influenced by inflammation and increased synthesis of albumin has also been found in some patients despite low S-albumin levels.

(3) Bilirubin may be increased due to cholestasis, hepatocellular failure or extra hepatic causes such as haemolysis.

(4) The large reserve capacity for conjugation and excretion of bilirubin in the liver as well as extra hepatic elimination makes bilirubin an insensitive marker of liver failure.

(5) Prothrombin time is increased due to decreased hepatic synthesis of the coagulation factors measured by the test, but is also influenced by e.g. vitamin K deficiency in cholestatic liver disease.

(6) Prothrombin time may be decreased due to enzyme induction as in early stages of cholestatic chronic liver disease.

(7) In patients evaluated for classification purpose, it is important that impaired hepatic function and not some other underlying disease is the cause of alterations in the Child-Pugh components.

(8) When available, biopsies can be used to confirm the diagnosis.

Art. 16. - (1) Despite the limitations mentioned above, the use of markers like serum albumin, prothrombin time and bilirubin is encouraged and abnormalities in these parameters may be better related to drug elimination capacity than other components of the Child-Pugh classification, e.g. encephalopathy and ascites.

(2) If the Child-Pugh classification is used, it must be assured that the subjects included in the study have an adequate range of decrease in serum albumin and increase in serum bilirubin and prothrombin time.

Alternative approaches

Art. 17. - (1) One way to ensure that the subjects to be studied actually have an impaired metabolic capacity, would be to administer, for instance, a CYP3A4 probe medicinal product (if the medicinal product under investigation is a CYP3A4 substrate) to the subjects to be included to observe if the pharmacokinetics of the probe medicinal product is altered (like a "positive control" known to be specially sensitive to liver impairment).

(2) This probe would have to be sensitive enough to identify a range of severity in hepatic dysfunction.

Art. 18. - (1) Exogenous markers that have been used to assess different hepatic drug elimination mechanisms are antipyrine, MEGX (lidocaine metabolite), ICG (indocyanine green) and galactose.

(2) Such markers may be used in parallel with the Child-Pugh classification and a justification for the choice of marker(s) should be given.

Art. 19. - (1) In conclusion, until optimal markers have been found, the Child-Pugh classification system can be used to categorise the degree of hepatic impairment of subjects included in a pharmacokinetic study and can, together with its individual components, be used in the evaluation of the pharmacokinetic results.

(2) The sponsor should submit all individual scores of the subjects included in the study, as well as other information on subjects' characteristics, e.g. results of standard laboratory tests.

IV.2. Study population

Art. 20. - (1) It may not be feasible to conduct the study in patients with the condition for which the medicinal product is indicated. An acceptable alternative is to use volunteers with hepatic disease.

(2) It is acknowledged that recruitment of suitable subjects may pose a difficulty.

(3) The most common patient categories are subjects with viral hepatitis and alcoholic liver disease.

Art. 21. - (1) Subjects classified by the Child-Pugh system as having mild impairment could have a normal hepatic function and for the majority of drugs, clinically significant differences are more likely to be observed in subjects with moderate and severe impairment.

(2) The sponsor should, as far as possible, aim to include subjects in which altered pharmacokinetics of the medicinal product in question are likely to be detected (Section II.1).

(3) The type of hepatic disease in the study population should depend on the pharmacokinetic characteristics of the medicinal product under investigation.

Art. 22. - (1) A study design that includes only subjects with moderate impairment and healthy controls may be used to screen for significant effects.

(2) If a significant effect is detected in the studied group, the pharmacokinetics in subjects with milder and, if possible, more severe degrees of impairment need to be evaluated to propose dose recommendations for these groups.

Art. 23. - (1) A within-study control group is recommended, and it should be comparable with the hepatically impaired subjects with respect to age, gender, weight, genetic polymorphisms and other factors with significant potential to alter the pharmacokinetics.

(2) Factors like smoking and alcoholic intake should be controlled for as well.

(3) If a certain hepatic condition is especially prevalent in the target population, this should be reflected in the choice of subjects in the study.

(4) The use of historical controls instead of including a within-study control group with normal liver function is discouraged since such designs may mask a difference in pharmacokinetics of the medicinal product.

Art. 24. - (1) The number of subjects enrolled should be sufficient to detect clinically relevant pharmacokinetic differences.

(2) The “clinically relevant” difference should be pre-specified and justified on the basis of well-documented concentration-response relationship of the parent medicinal product and/or its metabolites.

IV.3. Drug administration

Art. 25. - (1) Single-dose studies are sufficient when the medicinal product and its active metabolites exhibit linear and time-independent pharmacokinetics.

(2) A multiple-dose study is desirable when the medicinal product or an active metabolite is known to exhibit non-linear or time-dependent pharmacokinetics.

(3) If there are indications that a reduction of the elimination capacity may result in dose-dependent elimination of the drug, a multiple dose design is favourable.

Art. 26. - (1) In single-dose studies, if the medicinal product has low first-pass extraction, the same dose can in most cases be administered to all subjects in the study, regardless of hepatic function.

(2) However, if the medicinal product shows a substantial first-pass effect due to extensive hepatic metabolism, a dose reduction should be considered in the hepatically impaired group(s) for safety reasons.

Art. 27. - (1) For multiple-dose studies, lower or less frequent doses may be needed to prevent accumulation of the medicinal product and/or metabolites to unsafe levels in subjects with reduced hepatic function.

(2) The duration of dosing should in general be long enough to achieve a steady state of the plasma concentration values.

(3) A loading dose strategy may be suitable to facilitate this, particularly if the elimination half-life is significantly prolonged in subjects with hepatic impairment.

Art. 28. - (1) It is acknowledged that in several cases multiple dose studies are not feasible in subjects with hepatic diseases for ethical and/or safety reasons.

(2) Sponsors should give adequate justification for not conducting a multiple dose study in cases where that is recommended on pharmacokinetic grounds.

IV.4. Sample Collection and Analysis

Art. 29. - (1) Plasma (or whole blood, as appropriate) samples should be analysed for parent medicinal product and any metabolites with known or suspected activity (therapeutic or adverse).

(2) Metabolites, identified as toxic in preclinical studies, which could be affected by hepatic function should be evaluated.

(3) Also, metabolites that are considered relatively inactive in patients with normal hepatic function may reach active/toxic levels if the accumulation of the metabolites is substantial; hence, evaluation of such metabolites should be considered.

(4) The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant pharmacokinetic parameters for parent medicinal product and its metabolites.

Art. 30. - If the medicinal product or metabolites exhibit a high extent of plasma protein binding, the pharmacokinetics should be described and analysed from the point of view of the unbound concentrations of the medicinal product and active metabolites in addition to total concentration.

Art. 31. - For chiral medicinal products, the analysis of the enantiomers should be considered as the metabolic profile for each enantiomer may be different in subjects with hepatic impairment.

IV.5. Population pharmacokinetics

Art. 32. - (1) A population pharmacokinetic approach, based on data from patients participating in phase II/phase III clinical trials, may be useful to assess the impact of hepatic diseases on the pharmacokinetics of a medicinal product.

(2) This approach may prove difficult in hepatic impairment due to the low prevalence of hepatic disease in the general population.

(3) Furthermore, if a large effect is considered likely, this will probably result in exclusion of patients with hepatic disease from phase III studies.

(4) Population pharmacokinetics may instead be used to confirm the absence of an effect of hepatic disease on the pharmacokinetics of the medicinal product.

(5) In these studies, patients with hepatic impairment should be identified and classified using the same criteria as discussed for conventional studies.

(6) Population analysis for this purpose should be pre-specified.

IV.6. Physiological based pharmacokinetic models

Art. 33. - (1) The use of Physiological based pharmacokinetic models, may be used as a tool.

(2) By modelling the different pathways of metabolism, blood flows and excretion routes, an adequate estimation of the effect may be estimated and an optimised study design with respect to dose and duration of the study may be obtained.

IV.7. Pharmacodynamic assessments

Art. 34. - (1) Knowledge about the PK/PD relationships for efficacy and safety is important for the risk assessment and for development of appropriate dosing recommendations.

(2) The pharmacodynamics could be altered in hepatic impairment, which could lead to a change in the PK/PD relationship.

(3) When possible, it is recommended that assessment of pharmacodynamic endpoints for efficacy or safety is included in the study.

CHAPTER V
Data analysis

Art. 35. - (1) The primary intent of the data analysis is to identify patients at risk and assess whether a posology adjustment is required for patients with impaired hepatic function.

(2) If so, dosing recommendations based on measures of hepatic function should be developed, when appropriate.

(3) The data analysis should include:

a) Estimation of pharmacokinetic parameters

b) Evaluation of the relationship between measures of hepatic function and the pharmacokinetic parameters

c) Assessment of whether posology adjustment is warranted in patients with impaired hepatic function and, if possible, development of specific dosing recommendations.

d) Assessment of alteration of the interaction profile.

V.1. Parameter estimation

Art. 36. - (1) Plasma concentration data should be analysed to estimate various parameters describing the pharmacokinetics of the medicinal product and its active or main metabolites.

(2) The pharmacokinetic parameters include the area under the plasma concentration curve (AUC), peak plasma concentration (C_{max}), terminal half-life ($t_{1/2}$) for both parent compound and metabolites.

(3) For parent compound also apparent clearance (CL/F) and for multiple-dose studies also trough minimum concentration (C_{min}) and fluctuation should be taken into account.

(4) When appropriate (i.e. when the medicinal product or its metabolites exhibit a relatively high extent of plasma protein binding), parameters should be expressed in terms of unbound as well as total concentrations.

V.2. Presentation of data

Art. 37. – Data should be presented in several ways:

a) The graphical description of the relationship between measures of hepatic function and pharmacokinetic parameters may include the Child-Pugh classification (according to group and individual scores), its individual components (S-albumin, S-bilirubin, prothrombin time) and other markers, if used.

b) Descriptive statistics (e.g. mean, SD, range, median) of the pharmacokinetic parameters according to the hepatic function groups included in the study (normal, mild, moderate, and severe hepatic impairment).

c) Modelling of the relationship (linear or non-linear) between measures of hepatic function and pharmacokinetic parameters should be considered if a relevant marker is identified.

Art. 38. - (1) The pharmacokinetic parameters of interest are usually CL/F, AUC, C_{max} and C_{min} for the medicinal product and relevant

metabolites, when appropriate, expressed in terms of unbound concentrations.

(2) If different doses have been used within the study, AUC, C_{max} and C_{min} should be dose-normalised depending on the linearity of the pharmacokinetics.

(3) Other analysis/presentations may be required depending on a particular problem encountered.

V.3. Evaluation of Results and Development of Dosing Recommendations

Art. 39. - (1) Due to the limitations of hepatic markers it should be acknowledged that development of specific dosing recommendations may not always be possible.

(2) Factors that should be taken into account in evaluation of the data are the intended use of the drug, the pharmacokinetic characteristics of the drug in hepatic impairment and the PK/PD relationship regarding efficacy and safety.

(3) Based on available information regarding PK/PD for efficacy and safety, target criteria should be specified a priori for what change in pharmacokinetics would justify a posology adjustment.

(4) The target criteria should be based on the major concern (side effects or lack of efficacy) for the specific medicinal product.

(5) A thorough discussion of and justification for the chosen target as well as a description of how it was determined should be provided.

(6) The aim is to ensure that the major part of the patients will fulfil the target criteria.

Art. 40. - (1) Study results including the graphical description and a potential model for the relationships between hepatic function and relevant pharmacokinetic parameters should be used to construct specific dosing recommendations.

(2) Moreover, the variability in pharmacokinetics at different degree of hepatic function as well as possible differences in variability between "normal" hepatic function and decreased hepatic function should be taken into account.

Art. 41. - (1) Simulations can be used as a tool to identify doses and dosing intervals that achieve the target criteria for patients with different degrees of hepatic impairment.

(2) Simulations of the steady state exposure at the resulting recommended dose(s) could also be provided.

(3) The simulations may include graphical description of (total and, when relevant, unbound) concentration over time, also showing the predicted variability in the population.

(4) Graphical description of relevant steady state pharmacokinetic parameters versus hepatic function including appropriate measures for variability could also be supplied.

Art. 42. - (1) Consideration should also be given to possible consequences of altered importance of other elimination pathways and the interaction with concomitantly administered drugs.

(2) For pro-drugs (i.e., medicinal products with activity predominantly due to a hepatically generated metabolite), the plasma levels of the active substance may be decreased in patients with hepatic impairment and adjustments of the dose and/or dosing interval may be needed.

CHAPTER VI
Labelling

Art. 43. - The information in the SPC should follow the general guidelines outlined in the Notice to Applicants.

Art. 44. - (1) Specific dosing recommendations should be given in section 4.2 with cross-reference to section 5.2, and, when relevant, to sections 4.3 and/or 4.4.

(2) The characteristics of the subjects included in the hepatic impairment study should be stated in section 4.2 and extrapolations should not be made beyond what has actually been studied.

(3) Efforts should be made to describe the change in pharmacokinetics related to changes in clinical parameters like S-albumin, S-bilirubin or prothrombin time (preferably expressed in terms of the International Normalised Ratio, INR) if such a relationship has been found.

(4) Even when no posology adjustment is needed, this should be stated in section 4.2.

Art. 45. - (1) Lack of information regarding influence of hepatic impairment on the pharmacokinetics could result in a contraindication or warning, depending on the characteristics of the medicinal product.

(2) When precaution is recommended and no specific dose recommendations can be given, measures to be taken by the prescriber (e.g. careful monitoring) should be specified.

Art. 46. - (1) Information regarding the influence of hepatic impairment on the pharmacokinetics should be given in the *Special populations* subsection of section 5.2, with cross-reference to section 4.2 if posology adjustment is needed and 4.5 if interactions may be changed.

(2) The information should include which type of hepatic disease has been studied, effects on parent compound and metabolites and, when relevant, include effects on protein binding and unbound exposure.

Art. 47. - (1) Also when pharmacokinetics in patients with hepatic impairment has not been evaluated, this information should be given in section 5.2.

(2) When relevant and if this has been well justified, information that hepatic impairment is unlikely to affect the pharmacokinetics to a clinically relevant extent could be included.

ANNEX 1

Child-Pugh Classification

Assessment	Degree of abnormality	Score
Encephalopathy	None Moderate Severe	1 2 3
Ascites	Absent Slight Moderate	1 2 3
Bilirubin (mg/dL)	< 2 2.1 – 3 > 3	1 2 3
Albumin (g/dL)	> 3.5 2.8-3.5 <2.8	1 2 3
Prothrombin time (seconds > control)	0-3.9 4-6 >6	1 2 3

Total score	Group	Severity
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe