UNIVERSIDADE D
COIMBRA

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Assessment of the Effect of Hepatic Impairment on Pharmacokinetics

Dissertação no âmbito do Mestrado em Biotecnologia Farmacêutica orientada pelo Professor Doutor Sérgio Paulo de Magalhães Simões e pelo Professor Doutor José Luís de Almeida e apresentada à Faculdade de Farmácia da Universidade de Coimbra.

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Abstract

Pharmacokinetics is usually referred to as the study of the actions of the body on a drug. It includes four major processes: absorption, distribution, metabolism and excretion. It is highly influenced by several factors, of particular interest when considering the heterogeneity of the world population. This is the reason why pharmacokinetic studies are a critical requirement during drug's development process.

Liver plays an essential role on pharmacokinetics. It is greatly involved in its major processes and it is one of the main organs responsible for the metabolism and excretion of drugs. However, liver function is diminished in some diseases which makes these patients more susceptible to drug toxicity. Choosing an appropriate dosing regimen may be particularly difficult. Furthermore, there are different levels of hepatic impairment and various enzymes involved in the metabolism and excretion of specific drugs which leads to different types of impact on pharmacokinetics. Therefore, patients with hepatic impairment are an important subgroup of the population where pharmacokinetic studies should be thoroughly performed. There are specific guidelines for the conduction of clinical trials specific for this population of patients, aiming to understand and/or quantify that impact.

As the burden of liver disease in the world increases and there is a lack of markers for characterizing hepatic function regarding the prediction of drug elimination, the need for scientific development in this field rises as well.

The aim of this work is to review the involvement of the liver in the whole pharmacokinetics process and to understand the consequences of liver impairment in this process and its repercussion on drug development and clinical studies. In this context, the regulatory framework of this area will be analyzed both in the perspective of the European Medicines Agency and the Food and Drug Administration.

Keywords: Hepatic impairment; Liver disease; Pharmacokinetics; Dose adjustment; Regulatory framework.

Resumo

A farmacocinética é normalmente descrita como o estudo das ações de um fármaco no organismo. Inclui quatro processos principais: absorção, distribuição, metabolismo e excreção. É altamente influenciada por vários fatores, o que é particularmente interessante considerando a heterogeneidade da população mundial. Esta é a razão pela qual os estudos de farmacocinética representam uma necessidade crítica no desenvolvimento de um medicamento.

O fígado tem um papel essencial na farmacocinética. Está envolvido nos seus processos mais importantes e é um dos órgãos principais responsáveis pelo metabolismo e excreção de fármacos. No entanto, a função do fígado encontra-se diminuída em algumas doenças, o que torna estes sujeitos mais suscetíveis a toxicidade medicamentosa. Escolher um regime de dose apropriado pode ser particularmente difícil. Além disso, existem vários níveis de insuficiência hepática e várias enzimas envolvidas no metabolismo e excreção de certos fármacos, o que resulta em diferentes níveis de impacto na farmacocinética. Assim, doentes com insuficiência hepática são um subgrupo importante a onde estudos farmacocinéticos devem ser conduzidos. Existem *guidelines* específicas para a realização deste tipo de ensaios e para esta população de doentes, cujo objetivo é compreender e/ou quantificar este impacto.

Com o aumento do peso das doenças hepáticas no mundo e a falta de marcadores para a caracterização da função hepática com a capacidade de prever a eliminação de fármacos, uma necessidade de desenvolvimento científico também cresce.

O objetivo deste estudo é rever o envolvimento do fígado em todo o processo da farmacocinética e compreender as consequências da insuficiência hepática no mesmo e a sua repercussão no desenvolvimento de fármacos e ensaios clínicos. Neste contexto, o enquadramento regulamentar também será analisado, tanto da perspetiva da *European Medicines Agency* como da *Food and Drug Administration*.

Palavras-chave: Insuficiência hepática; Doenças hepáticas; Farmacocinética; Ajuste de dose; Enquadramento regulamentar.

List of Abbreviations

ACLF – Acute-on-chronic Liver Failure

ALF – Acute Liver Failure

AUC – Plasma Concentration Curve

CLF – Chronic Liver Failure

CL/F – Apparent Clearance

CL_H – Hepatic Clearance

CL_{INT} – Intrinsic Clearance

CL_{NR} – Non-renal Clearance

CL_R – Renal Clearance

C_{max} – Maximum Concentration/Peak Plasma Concentration

C_{min} – Minimum Concentration

df – Discriminant Function

E – Hepatic Extraction Ratio

EMA – European Medicines Agency

FDA – Food and Drug Administration

f_u – Fraction of Unbound Drug

HI – Hepatic Impairment

HIV-1 – Human Immunodeficiency Virus Type 1

ICG – Indocyanine Green

MELD – Model for End-stage Liver Disease

NCI – National Cancer Institute

PBPK – Physiologically Based Pharmacokinetic

PK/PD – Pharmacokinetics/pharmacodynamics

Q – Hepatic Blood Flow/Hepatic Perfusion

SmPC – Summary of Product Characteristics

$T_{1/2}$ – Terminal Half-life

V_d – Volume of Distribution

WHO – World Health Organization

Table and Figure Index

1. Introduction

The liver is one of the largest and most important organs in the body and it is responsible for a number of vital functions, both synthetic and metabolic. For instance, among others, it is responsible for the storage of glycogen, the biotransformation of nutrients, the detoxification of the body from harmful substances and the phagocytosis of bacteria and old white and red blood cells. (Kuntz e Kuntz, 2006)

Despite not being as prevalent as other diseases such as renal failure, liver diseases are an important and increasing cause of death worldwide. Cirrhosis and liver cancer (consequence of viral infections and substance abuse, among other reasons) alone currently comprise about 2 million deaths per year worldwide, which translates to about 3.5% of all deaths. (Asrani *et al.*, 2019)

The burden of liver disease is at its highest in Europe. In Northern European countries, liver disease mortality has been growing over the last decades, whereas in Southern Europe, it has declined. This heterogeneity is the consequence of the different prevalence of risk factors such as alcohol consumption and viral hepatitis. (Pimpin *et al.*, 2018) Similarly, in the United States, chronic liver disease and cirrhosis have been ranked as one of the top causes of death. (Rahimi e Rockey, 2016)

Liver failure progresses over the consecutive stages of inflammation (in this early stage, the liver is enlarged or inflamed), fibrosis (scar tissue begins to replace healthy tissue in the inflamed liver, cirrhosis (severe scarring has built up, making it difficult for the liver to function properly), end-stage liver disease (liver function has deteriorated to the point where the damage can't be reversed other than with a liver transplant) and finally liver cancer (the development and multiplication of unhealthy cells in the liver can occur at any stage of liver failure, although people with cirrhosis are more at risk). (Kuntz e Kuntz, 2006) So, as there are different degrees of hepatic impairment, they also impact vital functions on different levels. (Diep, Chudow e Sunjic, 2017)

Pharmacokinetics is the study of the interactions between the body and the drug, usually divided in four stages: absorption, distribution, metabolism and excretion. In disease conditions, these interactions are modified and not always on a quantifiable extent, meaning that all the pharmacokinetics properties studied for a specific drug in subjects with no decreased in liver function, can't be transposed to subjects with hepatic impairment. (Shargel e Yu, 2016)

The liver is one of the most essential organs in pharmacokinetics and the production of bile, the synthesis of plasma proteins (e.g., albumin, fibrinogen, globulins, heparin and coagulation factors) and metabolism of drugs, are the most important liver functions in the context of pharmacokinetics, as explained further on. Moreover, the liver's very own dual blood supply influences drug elimination. (Diep, Chudow e Sunjic, 2017)

Thus, as the liver plays a crucial role in the pharmacokinetics of drugs, a change in liver function, namely in liver diseases, is going to significantly impact how said drug will be absorbed, distributed, metabolized and eliminated. (Diep, Chudow e Sunjic, 2017)

So, considering the prevalence of hepatic dysfunction and the fact that the liver plays a major role in pharmacokinetics, it is imperative that the effect of the different degrees of compromised hepatic function is properly assessed during the clinical development stages of the drug. (Diep, Chudow e Sunjic, 2017) (European Medicines Agency, 2005)

2. Hepatic Impairment

Hepatic impairment or insufficiency or liver failure is the inefficiency of the liver to execute its physiological functions. It can be categorized as acute or chronic. More recently, a third category has emerged: acute-on-chronic liver failure (ACLF). (Blasco-Algora *et al.*, 2015)

2.1. Chronic Liver Failure

The most common type hepatic impairment, chronic liver failure (CLF), progresses throughout a long course of time, taking months or even years to display its first symptoms. (Xing, 2017) It is the outcome of the progression of a pre-existing liver disease. CLF is, very often, the consequence of cirrhosis, which itself is caused by a long-term exposure to various toxins like alcohol or viral infections. (Wong e Huang, 2018) It is characterized by the replacement of healthy hepatic tissue with scar tissue. (Schuppan e Afdhal, 2008) In Western Europe, long-term alcohol abuse is the main etiologic factor, whereas in Eastern Europe it's viral hepatitis. In Central Europe, however, both factors are similarly prevalent. (Pimpin *et al.*, 2018)

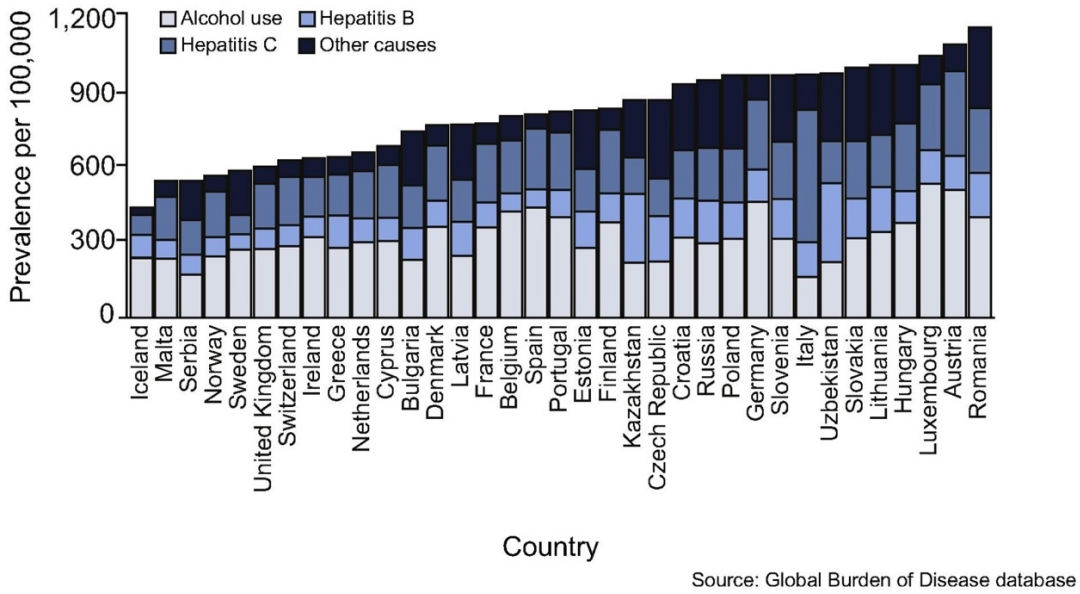

Figure 1: Age-standardized prevalence of cirrhosis and other liver diseases by etiology in 2016. (Pimpin *et al.*, 2018)

The most common alterations associated with chronic liver failure are the following:

– General symptoms: fatigue, apathy, lack of appetite, lack of concentration, malaise, sensation of repletion and meteorism.

– Changes in the color of stools and urine;

– Changes in the blood count (anemia, leucopenia, thrombocytopenia, macrocytosis);

– Fever;

– Splenomegaly. (Kuntz e Kuntz, 2006)

2.2. *Acute Liver Failure*

Acute liver failure (ALF), on the other hand, is the impairment of liver function that happens in a short period of time, generally days or weeks, in people without a pre-existing liver disease. (Xing, 2017) It is characterized by reduced hepatic function, jaundice and presence of hepatic encephalopathy. Acute liver failure develops when the regenerative capacity of the liver is surpassed by extent of cell death. (Khan *et al.*, 2006) Furthermore, According to the interval between onset of jaundice and development of encephalopathy, acute liver failure can be further classified as hyperacute liver failure (if the interval is between 0 and 7 days) and subacute liver failure (if the interval is >28 days). (Boyer, Manns e Sanyal, 2018)

Table 1: Prevalence of the causes of acute liver failure (Boyer, Manns e Sanyal, 2018)

Country	APAP (%)*[1]	HBV (%)*[1]	HAV (%)*[1]	Drug (%)	Indeterminate (%)	Others (%)
United Kingdom	73	2	2	2	8	9
France	2	32	4	17	18	27
Denmark	19	31	2	17	15	13
Argentina	0	22	8	14	25	31
Japan	0	18	3	0	71	8
India	0	31	2	5	0	62

*[1] APAP: acetaminophen; HBV: hepatitis B virus; HAV: hepatitis A virus.

Acute liver failure can be caused by many underlying conditions. Viral hepatitis is the most frequent worldwide. Infections with the hepatitis A, B and E virus are most prominent

in developing countries. In developed countries, acute liver failure is predominantly drug or toxin-induced, with acetaminophen/paracetamol being the leading cause. Other etiologies are metabolic, vascular or autoimmune diseases (*Table 1*). (Schilsky *et al.*, 2009) (Ichai e Samuel, 2011)

Some of the symptoms that may be associated with the presence of acute liver failure are the following:

- General symptoms: fatigue, loss of appetite, nausea, weakness, meteorism, apathy, disruption of the circadian rhythm;
- Encephalopathy;
- Cerebral edema;
- Jaundice;
- Hepatic fetor;
- Fever;
- Increased liver size. (Kuntz e Kuntz, 2006)

In addition to this, ACL also results in a number of variations in laboratory parameters, some of which are:

- Increased bilirubin;
- Decreased cholinesterase;
- Decreased electrolytes (hyponatremia and hypokalemia). (Kuntz e Kuntz, 2006)

2.3. Acute-on-Chronic Liver Failure

Acute-on-chronic liver failure is a recently described category (Xing, 2017), which is characterized by an acute decompensation of a pre-existing chronic liver disease. Organ failure is usually associated and it has a high short-term mortality rate (over 15% at 28 days). (Blasco-Algora *et al.*, 2015) (Rahimi e Rockey, 2016) There is still a lot of controversy and disagreement around this definition, as some consider it too vague. Alcoholic hepatitis, drug-induced liver injury and viral infections, as well as some endogenous factors (such as sepsis, diarrhea, hypoxia, among others) are usual causes of acute-on-chronic liver failure in both Eastern and Western countries. (Boyer, Manns e Sanyal, 2018) (Kuntz e Kuntz, 2006)

Acute-on-chronic liver failure is very similar to acute liver failure in terms of the clinical and laboratory parameters. (Kuntz e Kuntz, 2006)

3. Effect of Hepatic Impairment on Pharmacokinetics

The liver is one of the most important organs on pharmacokinetics, as it is heavily involved in all stages of drug disposition (absorption, distribution, metabolism and excretion). Therefore, any change in its functional status should be properly evaluated and characterized, in order to understand its consequences. Nonetheless, pharmacokinetic data on the function of the liver in people with hepatic impairment is still very limited and not always consistent. (Talal, Venuto e Younis, 2017) (Rowland e Tozer, 2010)

In addition to this, hepatic impairment can also alter the pharmacokinetics of drugs that are not primarily metabolized by the liver considering liver disease can influence renal performance. (Shargel e Yu, 2016)

3.1. Pharmacokinetic Changes in Hepatic Impairment

Drug disposition is particularly important when evaluating the impact of hepatic impairment on pharmacokinetics. The type and the degree of hepatic impairment influence, not only drug disposition, but also the physiological and pharmacological properties of the specific drug (e.g. binding to plasma proteins and hepatic extraction ratio). (Talal, Venuto e Younis, 2017) Therefore, it is important to assess the individual impact of each of these variables so that the appropriate dosage adjustment can be performed in patients with impaired hepatic function.

Acute liver failure is characterized by having a disseminated necrosis in the liver. However, hepatic dysfunction is not usually as serious as in chronic liver failure. Thus it doesn't always affect drug pharmacokinetic parameters in a significant way. (Rowland e Tozer, 2010)

On the other hand, chronic liver failure, more specifically cirrhosis, influences pharmacokinetics on an important level. The liver tissue is irreversibly damaged resulting in a reduction of hepatic blood flow and of the number of functional enzymes. (Palatini e Martin, De, 2016)

3.1.1. Absorption

3.1.1.1. First Pass Metabolism

Drugs that are administered through the gastrointestinal tract must cross the liver before they reach the systemic flow. In this route, they are metabolized, reducing their bioavailability. This process is called first pass metabolism, first pass effect or pre-systemic metabolism. (Currie, 2018) Drugs with a high extraction ratio are more prone to undergo first pass metabolism. (Susla e Lertora, 2012)

Patients with hepatic impairment experience a deficiency in the first pass metabolism leading to a higher concentration of orally administered drugs reaching the systemic circulation. (Rowland e Tozer, 2010) (Diep, Chudow e Sunjic, 2017) (Verbeeck, 2008)

Cirrhotic patients also experience portosystemic shunting, a direct connection between the portal vein and the systemic circulation, bypassing the liver which means also partial bypass of drugs and significant increase in bioavailability. (Rowland e Tozer, 2010)

3.1.2. Distribution

3.1.2.1. Protein Binding Capacity

When reaching the blood stream, several drugs have the ability to bind to plasma proteins. The degree to which this binding occurs significantly influences pharmacokinetics. (Currie, 2018) Albumin is one of the most common plasma proteins with which drugs are conjugated. (Persky, 2013)

Patients with liver failure experience a deficiency on the synthesis of albumin leading to a diminished concentration. Thus, as the binding of drugs to albumin decreases, their volume of distribution increases and so does the clearance of drugs with low hepatic extraction. (Rowland e Tozer, 2010) (Diep, Chudow e Sunjic, 2017) (Verbeeck, 2008) This change in the volume of distribution makes determining the loading dose of a certain drug harder. (Shargel e Yu, 2016)

The volume of distribution (V_d) corresponds to the volume of plasma to which an administered drug is distributed to, considering that it exists through the body in the same concentration as in the plasma. (Verbeeck, 2008)

$$Vd = \frac{\text{total amount of drug in the body}}{\text{drug blood plasma concentration}}$$

3.1.3. Metabolism

3.1.3.1. Metabolizing Enzymes

Drugs commonly go through metabolic reactions such as oxidation, hydrolysis or reduction on a primary level (performed by major enzyme families such as the cytochrome P450), and conjugation on a secondary level. These reactions are usually sequential, which is why they are classified as phase I and phase II, respectively. However, drugs aren't necessarily metabolized by both types of reactions, or even on this specific order. (Persky, 2013) (Tozer e Rowland, 2016)

Acute liver failure affects mostly the phase II enzymes and chronic liver failure the phase I enzymes. However, considering chronic liver failure has a bigger impact on pharmacokinetics, phase I enzymes are the most affected overall. (Diep, Chudow e Sunjic, 2017) (Verbeeck, 2008) (Rowland e Tozer, 2010) CYP1A1, CYP2C19, CYP3A4 and CYP3A5 are reduced in hepatic impairment, whereas CYP2D6, CYP2C9 and CYP2E1 usually aren't as significantly affected (*Figure 2*). (Dasgupta, 2012) This impairment can result in a reduction in the rate of drugs' metabolism, leading to a longer half-life and potential toxicity. (Diep, Chudow e Sunjic, 2017) (Verbeeck, 2008) (Rowland e Tozer, 2010)

3.1.4. Excretion

3.1.4.1. Hepatic Blood Flow

One of the most critical roles of the liver is on a drug pharmacokinetics is on hepatic clearance. Hepatic clearance (CL_H) is the volume of blood that is cleared of a drug, by the liver, per unit of time. (Tozer e Rowland, 2016) It depends on two variables: hepatic blood flow or hepatic perfusion (Q) and hepatic extraction ratio (E), which itself depends on the fraction of the drug unbound in plasma (f_u) and intrinsic clearance (CL_{INT}). (Talal, Venuto e Younis, 2017) (Susla e Lertora, 2012)

$$\mathrm{CL_H} = \mathrm{Q} * \mathrm{E}$$

$$\mathrm{E} = \frac{\mathrm{f_u} * \mathrm{CL_{int}}}{\mathrm{Q} + \mathrm{f_u} * \mathrm{CL_{int}}}$$

The hepatic extraction ratio is a measure of the liver's efficiency in eliminating a drug from systemic circulation. Drugs with a high extraction ratio have a high intrinsic clearance, meaning they are quickly cleared from the blood stream, depending only on hepatic perfusion. (Brunton, Lazo e Parker, 2006) Consequently, they are more sensitive to hypotension, which is common in acute liver failure and leads to a decrease in hepatic blood flow, a reduction in hepatic clearance and a prolongation of the half-life of a drug which can result in toxicity. (Diep, Chudow e Sunjic, 2017) (Verbeeck, 2008) (Rowland e Tozer, 2010)

In addition to this, unlike other organs, the liver has two blood supplies: the hepatic arteries and the hepatic portal vein. The portal circulation connects the gastrointestinal tract to the liver (*Figure 2*). Many substances are absorbed through this system, like nutrients, hormones and drugs. (Boyer, Manns e Sanyal, 2018)

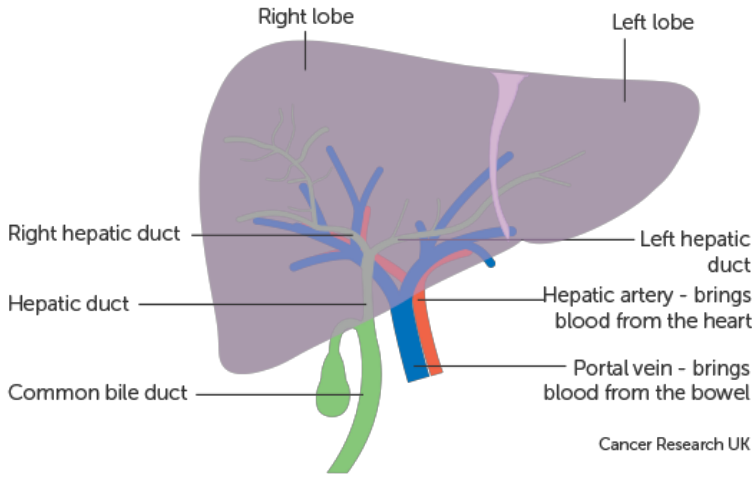

Figure 2: Hepatic Blood Supply (Cancer Research UK, 2019)

In patients with liver disease, scar tissue tends to accumulate in the liver, resulting in an altered liver architecture. As a consequence to this distortion, the hepatic blood flow is compromised. A higher pressure against the portal veins results in portal hypertension. Portal hypertension, similarly hypotension episodes, result in a decrease of hepatic blood flow. (Verbeeck, 2008)

3.1.4.2. Biliary Excretion

The gallbladder, alongside with the liver, plays an important role in pharmacokinetics. The hepatocytes produce bile – which essentially consists in water, bile salts, bile pigments, electrolytes, cholesterol and fatty acids – whereas the gallbladder stores it. Larger molecules

are typically conjugated and eliminated through the bile, while smaller ones tend to be eliminated by the kidneys, via urine. (Persky, 2013) (Tozer e Rowland, 2016)

Biliary excretion is compromised in patients with hepatic impairment. The resultant inefficiency of these processes is responsible for the accumulation of toxic metabolites, which itself can result in renal failure. (Shargel e Yu, 2016) (Persky, 2013)

4. Regulatory Perspective

Both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have recognized the importance of studying pharmacokinetics in subpopulations of patients. That's why both agencies have published specific guidelines for the conduct of pharmacokinetic studies on patients with hepatic impairment: EMA's "Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function" (European Medicines Agency, 2005) and FDA's "Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling". (Food and Drug Administration, 2003)

These guidelines provide a background to establish the scope and importance of harmonizing the recommendations of when and how pharmacokinetic studies are appropriate and necessary. Aside from small details, the two guidelines are concordant and follow, essentially, the same structure: establishment of when pharmacokinetic studies should be performed, considerations about the study design, recommendations on data analysis and how labelling should be accomplished. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

4.1. When to Perform Pharmacokinetic Studies

EMA recommends performing pharmacokinetic studies when the drug is likely to be used in patients with hepatic impairment, when hepatic impairment itself is expected to influence pharmacokinetics significantly (e.g. adefovir (European Medicines Agency, 2018) and tenofovir alafenamide (European Medicines Agency, 2017), used for the treatment of hepatitis B), or when posology requires adjustment for these patients considering the pharmacokinetics and pharmacodynamics reactions. (European Medicines Agency, 2005)

FDA, on the other hand, is more detailed: whenever hepatic metabolism and/or excretion is responsible for more than 20% of the elimination of a certain drug (e.g. fosamprenavir (European Medicines Agency, 2017) (Food and Drug Administration, 2017) and ritonavir (European Medicines Agency, 2019) (Food and Drug Administration, 2019)) pharmacokinetic studies should be performed. However, if the drug has a narrow therapeutic range (e.g. carbamazepine and warfarin (Tamargo, Heuzey, Le e Mabo, 2015)) pharmacokinetic studies should be performed even if the hepatic metabolism and/or excretion are responsible for less than 20% of its elimination. If the kidney or the lungs, in the case of gaseous or volatile drugs, are the only route of excretion, pharmacokinetic

studies aren't relevant. The same concept applies to drugs for single-dose administration. (Food and Drug Administration, 2003)

4.2. Classification of Hepatic Impairment

Despite both regulatory agencies agreeing that the Child-Pugh classification is, currently, the optimal method for categorizing the degrees of hepatic impairment, they also display some alternatives that fulfil the same objective. (European Medicines Agency, 2005) (Food and Drug Administration, 2003) For instance, EMA proposes the use of a probe drug of the enzyme for which the drug is a substrate, or the use exogenous markers such as antipyrine, MEGX, indocyanine green (ICG) and galactose. (European Medicines Agency, 2005) In addition to these, FDA also suggests the use of Maddrey discriminant function (df) and Mayo Survival Model for Primary Biliary Cirrhosis. (Food and Drug Administration, 2003)

4.3. Study Considerations

4.3.1. Study Population

EMA and FDA agree that the evaluation of potential effects can be achieved using only subjects with moderate impairment. If significant effects are identified, the assessment should be extended to patients with mild hepatic impairment and, if possible, severe impairment, according to European agency. The Child-Pugh classification is recommended by both agencies as the method to classify hepatic impairment. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

An appropriate control group (similar to the target population in terms of age, gender, weight and genetic polymorphisms) is recommended in order to properly assess the observed effects. Sponsors should, also, take into account the influence of other factors which can potentially affect pharmacokinetics, such as smoking, alcoholic intake, concomitant medications, ethnicity or any hepatic condition that is prevalent in the target population. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

4.3.2. Drug Administration

Both EMA and FDA agree that a single-dose study may be sufficient to determine the impact of hepatic impairment on pharmacokinetics, if the drug and its active metabolites

evidence a linear or time-independent pharmacokinetics. Multiple-dose studies are required when the drug and its active metabolites display a non-liner or time-dependent pharmacokinetics. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

Both regulatory agencies recommend dose reduction in subjects with a higher degree of hepatic impairment, if the drug has a substantial first pass metabolism, to prevent toxicity. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

4.3.3. Sample Collection and Analysis

The two guidelines provide recommendations on what substances should be analyzed in plasma: the parent drug and metabolites (identified as toxic in the preclinical development of the drug, as well as metabolites that may reach toxic levels in the presence of liver disease). Furthermore, if they demonstrate a high extent of plasma protein binding, the pharmacokinetics should be described regarding the unbound concentrations of these substances, along with total concentrations. For chiral drugs, both agencies recommend the study of the metabolic profile of the enantiomers. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

4.3.4. Population Pharmacokinetics and Physiological Based Pharmacokinetic Models

A population pharmacokinetics approach in patients enrolled in phase II or phase III clinical trials is acceptable. This design may also be used to confirm that no dosage adjustment is necessary, in case of absence of significant effects on pharmacokinetics of subjects with impaired hepatic function. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

EMA recognizes the use of physiological based pharmacokinetic models for estimating the effect of hepatic impairment in pharmacokinetics. (European Medicines Agency, 2005)

4.3.5. Pharmacodynamic Assessments

The evaluation of the pharmacokinetics/pharmacodynamics (PK/PD) relationship is important, as pharmacodynamics can be influenced by hepatic impairment. Thus, this assessment could be essential when developing dosing adjustments. Both agencies

recommend the evaluation of pharmacodynamic endpoints for safety and efficacy. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

4.4. Data Analysis

Data analysis' primary objective is to recognize patients at risk and determine the need for a dose adjustment. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

4.4.1. Parameter Estimation

Plasma concentration data should be analysed to estimate pharmacokinetic parameters of both the drug and its active metabolites. Such parameters are the plasma concentration curve (AUC), the peak plasma concentration (C_{max}), the terminal half-life ($t_{1/2}$) and the apparent clearance (CL/F). EMA adds that it is relevant to estimate the minimum plasma concentration (C_{min}) in multiple dose studies and FDA also highlights the importance of renal clearance (CL_R) and non-renal clearance (CL_{NR}). (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

When the parent drug or the metabolites are highly bound to plasma proteins, these parameters should be expressed in terms of unbound and total concentrations. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

4.4.2. Dosing Recommendations

FDA states that dosage adjustments shall be described in the label. When hepatic impairment doesn't influence pharmacokinetics and such adjustments are not necessary, this should also be indicated in the label and supported with relevant data. (Food and Drug Administration, 2003)

EMA also recognizes the difficulty in developing recommendations for dose adjustment in some cases. In addition to this, the variability between subjects with normal liver function and different degrees of reduced hepatic liver function should be assessed. Simulations can be used to estimate posology for patients with impaired hepatic function. Potential consequences to others routes of elimination, as well as interactions with concomitant medication should also be taken into account. (European Medicines Agency, 2005)

4.5. Labeling

EMA describes the information that shall be included in the label regarding patients with hepatic impairment as listed below:

- Specific dosing recommendations;
- Characteristics of the subjects included in the hepatic impairment study conducted;
- Changes observed in clinical parameters like S-albumin, S-bilirubin or prothrombin time (preferably in terms of INR). (European Medicines Agency, 2005)

If there is no information to support dose adjustment, depending on the characteristics of the drug, it could be contraindicated in patients with impaired hepatic function. The label should indicate the measures to be taken by the prescriber in this event. (European Medicines Agency, 2005)

If a drug doesn't need any dose adjustment, this should still be mentioned in the label. (European Medicines Agency, 2005)

Similarly, FDA proposes the information that should be included in the pharmacokinetic and special populations sections of the label.

- Mechanism of hepatic elimination;
- Percentage of drug that is eliminated by these mechanisms;
- Disposition of active metabolites;
- Effects on proteins binding of parent drug and metabolite;
- Effects on the stereospecific disposition on enantiomers in a racemic drug;
- Pharmacokinetic changes found in patients;
- Issues of altered pharmacodynamics and dosing adjustment required for patients. (Food and Drug Administration, 2003)

In addition to this, the American agency shows some examples of the wording to be used in these sections. (Food and Drug Administration, 2003)

4.6. Studies in Patients with Impaired Hepatic Function: the Challenges

Although both EMA's and FDA's guidelines provide detailed recommendations on hepatic impairment clinical trials, some difficulties emerge when these suggestions are put into practice, most significantly when they are performed with oncologic drugs. (D'Cunha e Lin, 2018)

EMA recognizes that recruiting patients that meet the inclusion and exclusion criteria required by the pharmacokinetic study, while simultaneously complying with the recommendations provided by the guideline, might be a challenge. (European Medicines Agency, 2005) In addition to this, patients with impaired hepatic function often simultaneously experience renal failure (Delcó *et al.*, 2005) which may make it difficult to determine whether the changes observed were caused by the hepatic or the liver impairment. Finally, ethical issues might compromise the conduction of some studies, particularly multiple dose studies in subjects with hepatic diseases. (European Medicines Agency, 2005)

5. Dose Adjustment

Considering the influence of the pharmacokinetic changes due to impaired hepatic function in the safety and efficacy of drugs administered to these patients, an appropriate dose adjustment must be carried out. However, unlike renal failure, where creatinine levels can be used to monitor the extent of renal damage, there is no similar marker that can be used in liver disease. (Delcó *et al.*, 2005)

5.1. Classification of Hepatic Impairment

5.1.1. The Child-Pugh Classification

The Child-Pugh classification is the most used method to evaluate the degree of hepatic impairment. (Talal, Venuto e Younis, 2017) It evaluates five parameters: encephalopathy, ascites, serum albumin, serum bilirubin and prothrombin time. To each of these variables, a scored (from 1 to 3 points) is assigned, considering its degree of abnormality, and later classified in one of three degrees of impairment: mild, moderate and severe (*Tables 2 and 3*).

However, the Child-Pugh classification has not been modified ever since its implementation, 50 years ago, and it was not originally designed to predict drug elimination capacity. Furthermore, none of the parameters evaluated is specific for liver failure, meaning that any change in them is not necessarily related to hepatic dysfunction, (European Medicines Agency, 2005) for example:

- Lower levels of albumin could be associated with a reduction of its production by hepatocytes in chronic liver disease, or it could be a result of inflammation. In addition to this, low levels of serum albumin aren't necessarily associated with a decrease in its production;
- Lower levels of bilirubin may be a result of cholestasis or hepatocellular failure, or they could be the consequence of extrahepatic causes like hemolysis. (European Medicines Agency, 2005)

Still, regardless of the fact that both EMA and FDA recommend the use of the Child-Pugh classification as a guide for dose adjustment, not many drugs have specific recommendations for dose adjustment based on this score. Furthermore, patients with severe hepatic impairment are not always included in pharmacokinetic studies during drug development due to ethical problems. (Verbeeck, 2008)

Table 2: The Child-Pugh Classification (Susla e Lertora, 2012)

Assessment	Degree of Abnormality	Assigned Score
Encephalopathy Grade*[2]	0	1
	1 or 2	2
	3 or 4	3
Ascites	Absent	1
	Slight	2
	Moderate	3
Serum Albumin (g/dL)	>3,5	1
	2,8-3,5	2
	<2,8	3
Serum Bilirubin (mg/dL)	1-2	1
	2-3	2
	>3	3
Prothrombin Time (seconds > control)	1-4	1
	4-10	2
	>10	3

Classification of Clinical Severity			
Total Points	5-6	7-9	>9
Clinical Severity	Mild	Moderate	Severe

Table 3: Classification of encephalopathy grade according to Child-Pugh classification (Susla e Lertora, 2012)

***[2] Encephalopathy Grade**	
Grade 0	Normal consciousness, personality, neurological examination, EEG
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, impaired hand writing, 5 cps waves on EEG
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves on EEG
Grade 4	Unrousable coma, no personality/behavior, decerebrate, slow 2- to 3-cps delta waves on EEG

5.1.2. Alternatives to the Child-Pugh Classification

There are other scores used to classify hepatic impairment in different degrees, like the National Cancer Institute (NCI) index, the model for end-stage liver disease (MELD) score or the Mayo risk scores for primary biliary cirrhosis and primary sclerosing cholangitis. Nonetheless, similarly to the Child-Pugh classification, none of these scores was created to establish a relationship between hepatic impairment and pharmacokinetics. (Talal, Venuto e Younis, 2017)

In the absence of Child-Pugh classification-based dose adjustment recommendations, *Appendix 1* provides some suggestions. (Verbeeck, 2008)

Nowadays, there are no adequate markers that can accurately predict drug elimination capacity in hepatic impairment. (European Medicines Agency, 2005) This is one of the obstacles in appropriately adjust dosing in subjects with impaired hepatic function, as now it is achieved empirically. (Diep, Chudow e Sunjic, 2017)

All things considered, a new method for evaluating hepatic impairment taking into account the pharmacokinetic perspective is an urgent need so that dose adjustments can evolve from an empiric assessment to an objective calculation. (Talal, Venuto e Younis, 2017)

5.2. Tools to Support Dose Adjustment

In addition to the previously mentioned tools, the World Health Organization (WHO) has also published a list of drugs (*Appendix 2*) with specific recommendations for patients with liver disease, to help prescribers. (World Health Organization, 2008) However, these recommendations are too ambiguous and may lead to heterogeneity due to the subjectivity of interpretation from different physicians.

5.3. Physiologically Based Pharmacokinetic Modeling

The idea of physiologically based pharmacokinetic (PBPK) modeling dates all the way back to 1937, when Torsten Teorell first introduced the concept of simulating pharmacokinetic data through biological and physiological components. (Jones e Rowland-Yeo, 2013)

PBPK models are mathematical models used to predict pharmacokinetic parameters of a drug, such as clearance, volume of distribution, effective half-life, among others. They

are made up of different compartments, each compartment corresponding to a tissue of the body, such as adipose, bone, gut, heart, kidney, liver, lung, muscle, skin and spleen. Each tissue is defined by tissue volume or weight and tissue blood flow rate. In addition to this, some drug-specific parameters, like intrinsic clearance, are also necessary in order to accurately reproduce concentration-time profiles. (Jones e Rowland-Yeo, 2013) (Beard, 2012)

PBPK modeling can be used from the early to the late stages of drug development. Thus, these models can potentially contribute to the estimation of the necessary dose adjustment for patients with impaired hepatic function, through an extrapolation made from the dose used in healthy volunteers. (Jones e Rowland-Yeo, 2013)

The insufficiency of enzymes, transporters, proteins and other parameters, as well as the lack of physiologic and biologic information on ethnic populations and diseases are some of the biggest challenges faced while using these models. However, when properly refined, they could expand the potential applications of these simulations. (Jones e Rowland-Yeo, 2013) (Jamei, 2016)

Nonetheless, despite the fact that these models have been around for quite some time, only recently have they had a more widespread use due to their complexity. (Jones e Rowland-Yeo, 2013)(Jones e Rowland-Yeo, 2013)

Therefore, both EMA and FDA have recognized the emergence and importance of PBPK modeling. Both agencies have recently published guidelines regarding these prediction models: EMA's "Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation" (December 2018) (European Medicines Agency, 2018) and FDA's Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry (August 2018). (Food and Drug Administration, 2018) These guidelines provide recommendations on the format, content and reporting of the results obtained from PBPK modeling.

The increasing application of PBPK modeling on drug development has been led by the rising of platforms that incorporate the principles of these models. Some examples are Simcyp® Population-Based Simulator, GastroPlus® and PKSIM®. (Jones e Rowland-Yeo, 2013)

5.4. The Pharmaceutical Industry Reality: Drugs Approved by EMA and FDA in 2018

As the liver plays an essential role in pharmacokinetics, hepatic impairment can affect the absorption, metabolism and elimination of many drugs. (Diep, Chudow e Sunjic, 2017) Thus, it would be interesting to realize out of all the drugs approved in 2018 how many actually have specific dosing recommendations for this subgroup of patients.

5.4.1. European Medicines Agency (EMA)

EMA's "Human medicines highlights 2018" states that 84 drugs received positive opinions, as listed in *Appendix 3*. (European Medicines Agency, 2018)

Out of the 45 drugs where the impact of hepatic impairment was studied, 15 didn't study the impact of severe hepatic impairment, and 2 of those also didn't study the impact of moderate hepatic impairment on pharmacokinetics. The remaining 30 were the only ones to provide recommendations on all the degrees of hepatic impairment. Finally, 38 drugs either didn't have any mention to hepatic impairment, or didn't study the impact of hepatic impairment on pharmacokinetics at all (*Figure 4*). (European Medicines Agency, 2018)

EMA's "Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function" recommends performing pharmacokinetic studies when the drug is likely to be used in patients with hepatic impairment, when hepatic impairment itself is expected to influence pharmacokinetics significantly or when posology requires adjustment for these patients considering the pharmacokinetics and pharmacodynamics reactions. Deferiprone Lipomed® (European Medicines Agency, 2018), beclometasone/formoterol/glycopyrronium bromide Riarify® (European Medicines Agency, 2018), melatonin Slenyto® (European Medicines Agency, 2018) and ulipristal acetate Richter® (European Medicines Agency, 2018) are examples of drugs that are extensively metabolized by the liver, yet no pharmacokinetic studies on patients with hepatic impairment were conducted.

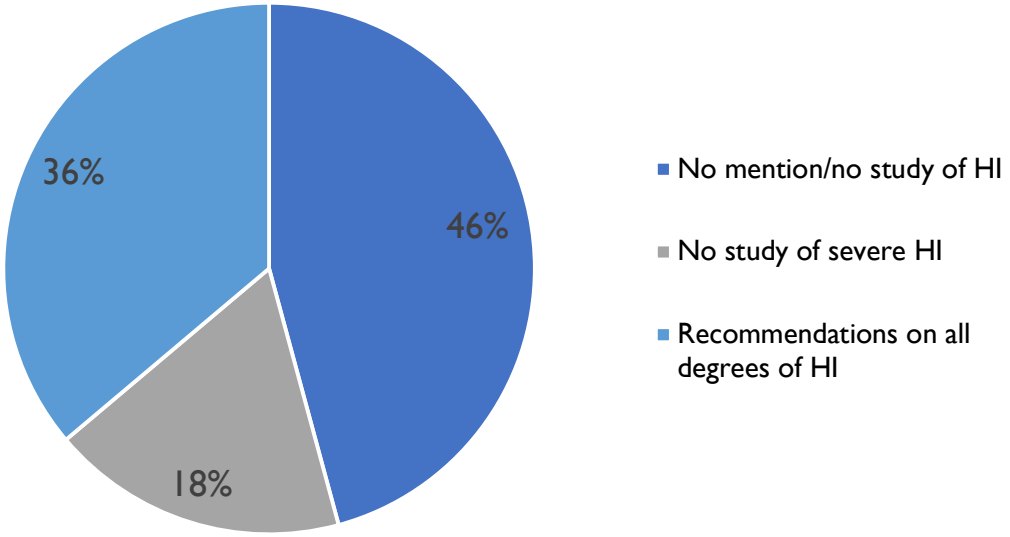

Figure 3: Hepatic impairment recommendations for drugs that received positive opinions by EMA in 2018 (HI – Hepatic impairment)

5.4.2. Food and Drug Administration (FDA)

According to FDA's "2018 New Drug Therapy Approvals", 59 drugs were approved throughout the year of 2018, as listed in *Appendix 4*. (Food and Drug Administration, 2018)

Out of the 38 drugs where the impact of hepatic impairment was studied, 17 didn't study the impact of severe hepatic impairment, and 6 of those also didn't study the impact of moderate hepatic impairment on pharmacokinetics. 4 drugs simply had no recommendations toward the higher degrees of hepatic impairment, not mentioning whether any pharmacokinetic studies were conducted or not, 1 of those mentioning a decrease of C_{max} and AUC but failing to provide any recommendations on how dosing should be adjusted. The remaining 17 were the only ones to provide recommendations on all the degrees of hepatic impairment. Finally, 21 drugs either didn't have any mention to hepatic impairment, or didn't study the impact of hepatic impairment on pharmacokinetics at all (*Figure 5*). (Food and Drug Administration, 2018)

FDA's "Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" recommends the conduction of pharmacokinetic studies on patients with impaired liver function if the drug is extensively metabolized or excreted by the liver or, even if the extent of hepatic elimination isn't as significant, if the drug has a narrow therapeutic range. Similarly to EMA, one of the

examples of drugs that didn't study the impact hepatic impairment on pharmacokinetics was stiripentol Diacomit® (Food and Drug Administration, 2018). Considering Diacomit® (Food and Drug Administration, 2018) is mainly metabolized by the liver, pharmacokinetic studies on patients with hepatic impairment should have been conducted in order to assess the impact and potential need for dose adjustment, which was not the case.

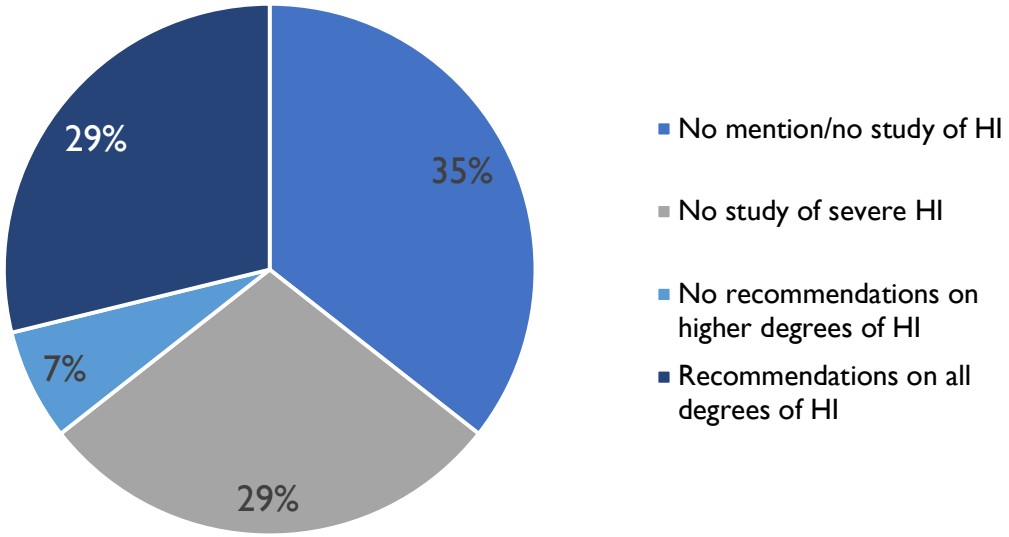

Figure 4: Hepatic impairment recommendations for drugs approved by FDA in 2018 (HI – Hepatic Impairment)

6. Case Study – Combined Therapy of Fosamprenavir and Ritonavir

6.1. Pharmacokinetic changes in hepatic impairment

6.1.1. *First Pass Metabolism*

Fosamprenavir and ritonavir is a drug combination used in for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) (European Medicines Agency, 2017) (European Medicines Agency, 2019) patients, who often have impaired liver function. (Price e Thio, 2010) According to the summary of product characteristics (SmPC), fosamprenavir's maximum concentration (C_{max}) is approximately 6.08 μg/ml (European Medicines Agency, 2017) and ritonavir's C_{max} 0.84 μg/ml (European Medicines Agency, 2019) (in a dosing regimen of 700 mg twice daily and 100mg once daily, respectively).

In patients with hepatic impairment, using the standard dosing regimen, the bioavailability of fosamprenavir and ritonavir increases leading to an increase in C_{max}. In mild hepatic impairment, fosamprenavir's C_{max} can go up 7.04 μg/ml and ritonivir's C_{max} up to 1.03 μg/ml (in a dosing regimen of 700 mg twice daily and 100 mg once daily). Similarly, in moderate hepatic impairment, fosamprenavir's C_{max} can go up 6.68 μg/ml and ritonivir's C_{max} up to 1.62 μg/ml (in a dosing regimen of 700 mg once daily and 100 mg once daily). (Pérez-Elías *et al.*, 2009) This can lead to consequences in toxicity and overdosing risk, which justifies adjustment of dosing in this subpopulation of patients.

6.1.2. *Protein Binding Capacity*

Both fosamprenavir and ritonavir have a >90% binding to plasma proteins alpha-1-acid-glycoprotein (AAG) and albumin. That being said, when administered to patients with hepatic impairment these two drugs will have a higher volume of distribution. (European Medicines Agency, 2017) (European Medicines Agency, 2019)

6.1.3. *Metabolizing Enzymes*

In the case of fosamprenavir and ritonavir, both drugs are extensively metabolized by CYP3A4. (European Medicines Agency, 2017) (European Medicines Agency, 2019) Because its activity is decreased in patients with hepatic impairment, fosamprenavir's and ritonavir's

metabolism may be compromised resulting in a significantly increased half-life and need for dose adjustment.

6.2. *Dose Adjustment*

For fosamprenavir's and ritonavir's combined therapy the Child-Pugh classification is used as a guide for dose adjustment, (European Medicines Agency, 2017) (Food and Drug Administration, 2017) as it is demonstrated in *Table 4*. No studies have been conducted in children and adolescents, so no dosing recommendations may be established. (European Medicines Agency, 2017) (Food and Drug Administration, 2017) (European Medicines Agency, 2019) (Food and Drug Administration, 2019)

Table 4: Dose adjustment recommendations for adults for fosamprenavir and ritonavir in Europe (SmPC) and in the United States (Label) (European Medicines Agency, 2017) (Food and Drug Administration, 2017)

Standard Posology for adults	**Mild hepatic impairment (Child-Pugh score 5-6)**	**Moderate hepatic impairment (Child-Pugh score 7-9)**	**Severe hepatic impairment (Child-Pugh score 10-15)**
Fosamprenavir 700 mg twice daily + Ritonavir 100 mg twice daily	Fosamprenavir 700 mg twice daily + Ritonavir 100 mg once daily	Fosamprenavir 450 mg twice daily + Ritonavir 100 mg once daily	Fosamprenavir 300 mg twice daily + Ritonavir 100 mg once daily

7. Conclusions

Just as the liver's functions are vast and complex, so are the diseases that can impair its functional status. Liver diseases are a very complex group of illnesses, very heterogeneous, with different etiologies and highly influenced by individual characteristics. Accordingly, the importance of liver impairment has been recognized, on the one hand because of its prevalence, and in the other hand, because of the need to study these subpopulations regarding pharmacokinetics and dosage adjustment of drugs. (Kuntz e Kuntz, 2006)

Pharmacokinetics is highly influenced by several factors, one of them being the functional status of the liver. The whole pharmacokinetics process changes in the presence of impaired hepatic function. From absorption, where the decrease in first pass metabolism increases the amount of drug that reaches the systemic circulation; to distribution, where the lower concentration of plasma proteins alters the volume of distribution of the drug; and metabolism and excretion, where a decrease in hepatic blood flow can impair drug clearance, smaller concentrations of enzymes can debilitate drug metabolism and a compromised biliary excretion can result in the accumulation of toxic metabolites. These alterations could be minor, as they usually are in acute hepatic impairment. But they can also be severely dangerous and detrimental. Even though, data on the pharmacokinetic capacity of the liver in hepatic diseases is insufficient and sometimes incoherent. (Talal, Venuto e Younis, 2017) (Rowland e Tozer, 2010)

EMA and FDA have both published guidelines that establish recommendations on when studies on patients with hepatic impairment should be conducted how to properly classify the degrees of hepatic impairment (currently accomplished, in the most part, by the Child-Pugh classification), how to design the study, how to analyze the data that results from these studies and how to properly address labeling. (European Medicines Agency, 2005) (Food and Drug Administration, 2003)

However, over a decade later, and despite the emergence of new simulation models to help predict the effect of hepatic impairment on the pharmacokinetics of a specific drug, or tools to aid prescribers in dose adjustment, the major difficulty associated with liver failure remains the same: the absence of a validated marker that can accurately determine the drug elimination capacity of patients with impaired hepatic function. Both regulatory agencies have acknowledged that the current methods used to evaluate the degree of hepatic impairment can't properly establish a relationship between the disease and the

pharmacokinetics, as they were not designed with that intent. (European Medicines Agency, 2005) (Food and Drug Administration, 2003) Without such a marker or system, dose adjustment can't be accomplished in a rigorous way and the pharmacokinetic studies performed in patients with hepatic impairment will not be improved. Taking this into account, the development of new methods to predict dosing adjustment in these patients is imperious. (Talal, Venuto e Younis, 2017)

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Appendix I – Dose Adjustment in Patients with Hepatic Impairment (Verbeeck, 2008)

Clinical setting	Recommendation
Drugs with a relatively high extraction ratio (>70%)	The dose should be reduced because the oral bioavailability can be significantly increased.
Drugs with a low hepatic extraction ratio (<30%) and high plasma protein binding (>90%)	Pharmacokinetic evaluations should be based on the unbound blood/plasma concentrations because the unbound fraction of drug may be significantly increased. Dosage adjustments may be necessary even though total blood/plasma concentrations are within the normal range.
Drugs with a low hepatic extraction ratio (<30%) and low plasma protein binding (<90%)	Dosage adjustment may be necessary and should be targeted at maintaining normal total (bound plus unbound) plasma concentrations.
The elimination of drugs partly excreted unchanged by the kidneys will be impaired in patients with hepatorenal syndrome	Consider that creatinine clearance significantly over estimates glomerular filtration rate in these patients.
The distribution volume of hydrophilic drugs may be increased in patients with edema or ascites	The loading dose may have to be increased if a rapid and complete response to the drug is required. Many of these drugs are eliminated by the kidneys so renal function should be taken into consideration.
Drug selection and dosing in patients with severe liver disease (Child-Pugh classification)	Use caution when administering drugs with narrow therapeutic indices to patients with liver disease and any drug to patients with severe liver disease.

Appendix 2 – WHO's table of dosing recommendations for hepatic impairment (World Health Organization, 2008)

Drug	Dosing Recommendations
Abacavir	Avoid in moderate hepatic impairment unless essential; avoid in severe hepatic impairment.
Acetylsalicylic acid	Avoid increased risk of gastrointestinal bleeding.
Alcuronium	Possibly slower onset, higher dose requirement and prolonged recovery time.
Allopurinol	Reduce dose.
Aluminium hydroxide	In patients with fluid retention, avoid antacids containing large amounts of sodium; also avoid those causing constipation (can precipitate coma).
Aminophylline	Reduce dose.
Amitriptyline	Sedative effects increased (avoid in severe liver disease).
Amodiaquine	Avoid.
Amoxicillin + Clavulanic acid	Monitor liver function in liver disease. Cholestatic jaundice reported either during or shortly after treatment; more common in patients over the age of 65 years and in males; duration of treatment should not usually exceed 14 days.
Artemether + Lumefantrine	Caution in severe impairment; monitor ECG and plasma potassium.
Azathioprine	May need dose reduction.
Azithromycin	Avoid; jaundice reported.
Bupivacaine	Avoid (or reduce dose) in severe liver disease.
Carbamazepine	Metabolism impaired in advanced liver disease.
Ceftriaxone	Reduce dose and monitor plasma concentration if both hepatic and severe renal impairment.
Chloramphenicol	Avoid if possible—increased risk of bone-marrow depression; reduce dose and monitor plasmachloramphenicol concentration.
Chlorphenamine	Sedation inappropriate in severe liver disease—avoid.
Chlorpromazine	Can precipitate coma; hepatotoxic.
Ciclosporin	May need dose adjustment.
Ciprofloxacin	Hepatic dysfunction reported.
Clindamycin	Reduce dose.
Clomifene	Avoid in severe liver disease.
Clomipramine	Sedative effects increased (avoid in severe liver disease).
Clonazepam	Can precipitate coma.
Cloxacillin	Cholestatic jaundice may occur up to several weeks after treatment has been stopped; administration for more than 2 weeks and increasing age are risk factors.
Codeine	Avoid or reduce dose—may precipitate coma.

Contraceptives, oral	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy.
Cyclophosphamide	Reduce dose.
Cytarabine	Reduce dose.
Dacarbazine	Dose reduction may be required in mild to moderate liver disease; avoid if severe.
Daunorubicin	Reduce dose.
Diazepam	Can precipitate coma.
Didanosine	Insufficient information but consider dose reduction.
Doxorubicin	Reduce dose according to bilirubin concentration.
Doxycycline	Avoid (or use with caution).
Efavirenz	In mild to moderate liver disease, monitor liver function; avoid in severe hepatic impairment.
Enalapril	Closely monitor patients with impaired liver function.
Ergometrine	Avoid in severe liver disease.
Ergotamine	Avoid in severe liver disease—risk of toxicity increased.
Erythromycin	May cause idiosyncratic hepatotoxicity.
Ether, anaesthetic	Avoid.
Ethinylestradiol	Avoid.
Etoposide	Avoid in severe hepatic impairment.
Fluconazole	Toxicity with related drugs.
Fluorouracil	Caution advised.
Fluphenazine	Can precipitate coma; hepatotoxic.
Furosemide	Hypokalaemia may precipitate coma (use potassium-sparing diuretic to prevent this); increased risk of hypomagnesaemia in alcoholic cirrhosis.
Glibenclamide	Increased risk of hypoglycaemia in severe liver disease; avoid or use small dose; can produce jaundice.
Griseofulvin	Avoid in severe liver disease.
Haloperidol	Can precipitate coma.
Halothane	Avoid if history of unexplained pyrexia or jaundice following previous exposure to halothane.
Heparin	Reduce dose in severe liver disease.
Hydralazine	Reduce dose.
Hydrochlorothiazide	Avoid in severe liver disease; hypokalaemia may precipitate coma (potassium-sparing diuretic can prevent this); increased risk of hypomagnesaemia in alcoholic cirrhosis.
Ibuprofen	Increased risk of gastrointestinal bleeding and can cause fluid retention; avoid in severe liver disease.
Indinavir	Reduce dose to 600 mg every 8 hours in mild to moderate hepatic impairment; not studied in severe impairment.
Iopanoic acid	Avoid in severe hepatic disease.
Isoniazid	Use with caution; monitor liver function regularly and particularly frequently in the first 2 months.

Levonorgestrel	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy.
Lidocaine	Avoid (or reduce dose) in severe liver disease.
Lopinavir + Ritonavir	Avoid oral solution because of propylene glycol content; use capsules with caution in mild to moderate hepatic impairment and avoid in severe impairment.
Magnesium hydroxide	Avoid in hepatic coma if risk of renal failure.
Magnesium sulfate	Avoid in hepatic coma if risk of renal failure.
Medroxyprogesterone	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy.
Mefloquine	Avoid for prophylaxis in severe liver disease.
Meglumine antimoniate	see Pentavalent antimony compounds.
Mercaptopurine	May need dose reduction.
Metformin	Withdraw if tissue hypoxia likely.
Methotrexate	Dose-related toxicity—avoid in non-malignant conditions (for example, rheumatic disorders).
Methyldopa	Manufacturer advises caution in history of liver disease; avoid in active liver disease.
Metoclopramide	Reduce dose.
Metronidazole	In severe liver disease, reduce total daily dose to one-third and give once daily.
Morphine	Avoid or reduce dose—may precipitate coma.
Nalidixic acid	Hepatic dysfunction reported; partially conjugated in liver.
Nelfinavir	No information available—manufacturer advises caution.
Nevirapine	Caution in moderate hepatic impairment; avoid in severe hepatic impairment.
Nifedipine	Reduce dose.
Nitrofurantoin	Cholestatic jaundice and chronic active hepatitis reported.
Norethisterone	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy.
Ofloxacin	Hepatic dysfunction reported; reduce dose in severe liver disease.
Paracetamol	Dose-related toxicity—avoid large doses.
Pentavalent antimony compounds	Increased risk of liver damage and hepatic failure in preexisting liver disease.
Phenobarbital	May precipitate coma.
Phenytoin	Reduce dose to avoid toxicity.
Prednisolone	Adverse effects more common.
Procainamide	Avoid or reduce dose.
Procarbazine	Avoid in severe hepatic impairment.
Promethazine	Avoid—may precipitate coma in severe liver disease; hepatotoxic.
Propranolol	Reduce oral dose.
Propylthiouracil	Reduce dose.
Pyrazinamide	Avoid—idiosyncratic hepatotoxicity more common.
Ranitidine	Increased risk of confusion; reduce dose.

Rifampicin	Impaired elimination; may be increased risk of hepatotoxicity; avoid or do not exceed 8 mg/kg daily.
Ritonavir	See Lopinavir + Ritonavir.
Saquinavir	Plasma concentration possibly increased; manufacturer of gel-filled capsules advises caution in capsules containing saquinavir mesilate advises caution in severe impairment moderate hepatic impairment and avoid in severe impairment.
Sodium nitroprusside	Avoid in severe liver disease.
Sodium valproate	see Valproic acid.
Sulfadiazine	Avoid if severe.
Sulfamethoxazole + Trimethoprim	Manufacturer advises avoid in severe liver disease.
Suxamethonium	Prolonged apnoea may occur in severe liver disease due to reduced hepatic synthesis of plasma cholinesterase.
Testosterone	Preferably avoid—possibility of dose-related toxicity and fluid retention.
Theophylline	Reduce dose.
Thiopental	Reduce dose for induction in severe liver disease.
Valproic acid	Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months).
Verapamil	Reduce oral dose.
Vinblastine	Dose reduction may be necessary.
Vincristine	Dose reduction may be necessary.
Warfarin	Avoid in severe liver disease, especially if prothrombin time already prolonged.
Zidovudine	Accumulation may occur.

Appendix 3 – List of drugs that received positive opinions by EMA in 2018 and dosing recommendations for hepatic impairment

Trade Name	Recomendation
Aimovig	No dose adjustment necessary. (European Medicines Agency, 2018)
Alpivab	No dose adjustment necessary. (European Medicines Agency, 2018)
Alunbrig	No dose adjustment necessary for mild and moderate HI. Dose adjustment for severe HI is described on the SmPC. (European Medicines Agency, 2018)
Amglidia	Dose adjustment for mild to moderate hepatic impairment is described on the SmPC. The use in severe HI is contraindicated. (European Medicines Agency, 2018)
Apealea	No dose adjustment necessary for mild HI. Dose adjustment for moderate and severe HI is described on the SmPC. (European Medicines Agency, 2018)
Besremi	No dose adjustment necessary in mild HI. The use in moderate and severe HI is contraindicated. (European Medicines Agency, 2018)
Bevespi Aerosphere	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Biktarvy	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Braftovi	Dose adjustment for mild HI is described on the SmPC. No recommendations can be made for moderate and severe HI. (European Medicines Agency, 2018)
Buvidal	The drug should be used with caution in moderate HI and is contraindicated in severe HI. (European Medicines Agency, 2018)
Cablivi	No dose adjustment necessary. (European Medicines Agency, 2018)
Carmustine Obvius	There are no specific recommendations for HI. (European Medicines Agency, 2018)
Deferiprone Lipomed	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Delstrigo	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (European Medicines Agency, 2018)
Dengvaxia	HI was not mentioned. (European Medicines Agency, 2018)
Duzallo	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Dzuveo	Use with caution in moderate and severe HI. (European Medicines Agency, 2018)
Emgality	No dose adjustment necessary. (European Medicines Agency, 2018)
Erleada	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Flucelvax Tetra	HI was not mentioned. (European Medicines Agency, 2018)

Fulphila	No studies were conducted. HI is not expected to affect pharmacokinetics. (European Medicines Agency, 2018)
Gefitinib Mylan	Monitor closely in patients with HI moderate and severe for adverse events. (European Medicines Agency, 2018)
Halimatoz	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Hefiya	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Hemlibra	No dose adjustment necessary in mild HI. There is limited data on moderate HI and severe HI was not studied. (European Medicines Agency, 2018)
Hulio	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Hyrimoz	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Ilumetri	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Imfinzi	No dose adjustment necessary. (European Medicines Agency, 2018)
Jivi	HI was not mentioned. (European Medicines Agency, 2018)
Juluca	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Kanjinti	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Kigabeq	No dose adjustment necessary. (European Medicines Agency, 2018)
Kymriah	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Lamzede	No dose adjustment necessary. (European Medicines Agency, 2018)
Lenalidomide Accord	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Lusutrombopag Shionogi	No dose adjustment necessary. (European Medicines Agency, 2018)
Luxturna	No dose adjustment necessary. (European Medicines Agency, 2018)
Macimorelin Aeterna Zentaris	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Mektovi	No dose adjustment necessary in subjects with mild HI. Moderate and severe HI were not studied. (European Medicines Agency, 2018)
Mepsevii	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Miglustat Dipharma	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Myalepta	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Mylotarg	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Namuscla	Use with caution in mild and moderate HI. The use in severe HI is

	contraindicated. (European Medicines Agency, 2018)
Nerlynx	No dose adjustment necessary in subjects with mild and moderate HI. The use in severe HI is not recommended. (European Medicines Agency, 2018)
Nityr	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Ogivri	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Onpattro	No dose adjustment necessary in subjects with mild HI. Moderate and severe HI were not studied. (European Medicines Agency, 2018)
Pelgraz	No studies were conducted. HI is not expected to affect pharmacokinetics. (European Medicines Agency, 2018)
Pelmeg	No studies were conducted. HI is not expected to affect pharmacokinetics. (European Medicines Agency, 2018)
Pemetrexed Krka	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Pifeltro	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Poteligeo	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Prasugrel Mylan	No dose adjustment necessary in subjects with mild and moderate HI. The use in severe HI is contraindicated. (European Medicines Agency, 2018)
Riarify	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Rizmoic	No dose adjustment necessary in subjects with mild and moderate HI. The use in severe HI is not recommended. (European Medicines Agency, 2018)
Rubraca	No dose adjustment necessary in subjects with mild HI. Moderate and severe HI were not studied. (European Medicines Agency, 2018)
Rxulti	Dose adjustment for severe HI is described on the SmPC. (European Medicines Agency, 2018)
Segluromet	The use in severe HI is contraindicated. (European Medicines Agency, 2018)
Semglee	In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism. (European Medicines Agency, 2018)
Shingrix	HI was not mentioned. (European Medicines Agency, 2018)
Silodosin Recordati	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Slenyto	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Steglatro	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Steglujan	No dose adjustment necessary in subjects with mild and moderate HI.

	Severe HI was not studied. (European Medicines Agency, 2018)
Symkevi	Dose adjustment for HI is described on the SmPC. (European Medicines Agency, 2018)
Takhzyro	No studies were conducted. HI is not expected to affect pharmacokinetics. (European Medicines Agency, 2018)
Tegsedi	No dose adjustment necessary in subjects with mild and moderate HI. The use in severe HI is contraindicated. (European Medicines Agency, 2018)
Tobramycin PARI	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Trazimera	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Trecondi	The SmPC isn't available because there is no marketing authorization yet. (European Medicines Agency, 2019)
Trydonis	No studies were conducted. HI is not expected to affect pharmacokinetics. (European Medicines Agency, 2018)
Udenyca	No studies were conducted. HI is not expected to affect pharmacokinetics. (European Medicines Agency, 2018)
Ulipristal Acetate Richter	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Vabomere	No dose adjustment necessary (European Medicines Agency, 2018)
Verzenios	No dose adjustment necessary in subjects with mild and moderate HI. Dose adjustment for severe HI is described on the SmPC. (European Medicines Agency, 2018)
Veyvondi	HI was not mentioned. (European Medicines Agency, 2018)
Vyxeos	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (European Medicines Agency, 2018)
Xerava	No dose adjustment necessary. (European Medicines Agency, 2018)
Yescarta	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Zessly	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)
Ziextenzo	No studies were conducted. HI is not expected to affect pharmacokinetics. (European Medicines Agency, 2018)
Zirabev	The pharmacokinetics in HI was not studied. (European Medicines Agency, 2018)

Appendix 4 – List of drugs that were approved by FDA in 2018 and dosing recommendations for hepatic impairment

Trade Name	Dosing Recomendations
Aemcolo	The pharmacokinetics in HI was not studied. (Food and Drug Administration, 2018)
Aimovig	No studies were conducted. HI is not expected to affect pharmacokinetics. (Food and Drug Administration, 2018)
Ajovy	No studies were conducted. HI is not expected to affect pharmacokinetics. (Food and Drug Administration, 2018)
Akynzeo	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe HI, for lack of studying. (Food and Drug Administration, 2018)
Annovera	The pharmacokinetics in HI was not studied. (Food and Drug Administration, 2018)
Asparlas	The impact of HI on is unknow. Avoid in severe HI. (Food and Drug Administration, 2018)
Biktarvy	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Braftovi	No dose adjustment necessary in mild HI. No recommendations for moderate and severe HI. (Food and Drug Administration, 2018)
Copiktra	No dose adjustment necessary. (Food and Drug Administration, 2018)
Crysvita	The pharmacokinetics in HI was not studied. (Food and Drug Administration, 2018)
Daurismo	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Diacomit	Not recommended in subjects with HI. (Food and Drug Administration, 2018)
Doptelet	No dose adjustment necessary. (Food and Drug Administration, 2018)
Elzonris	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Emgality	No studies were conducted. HI is not expected to affect pharmacokinetics. (Food and Drug Administration, 2018)
Epidiolex	Dose adjustment in HI described on the label. (Food and Drug Administration, 2018)
Erleada	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Firdapse	The pharmacokinetics in HI was not studied. (Food and Drug

	Administration, 2018)
Galafold	Hepatic impairment was not mentioned. (Food and Drug Administration, 2018)
Gamifant	No dose adjustment necessary. (Food and Drug Administration, 2018)
Ilumya	The pharmacokinetics in HI was not studied. (Food and Drug Administration, 2018)
Krintafel	The pharmacokinetics in HI was not studied. (Food and Drug Administration, 2018)
Libtayo	Not studied in patients with moderate and severe HI. (Food and Drug Administration, 2018)
Lokelma	Hepatic impairment was not mentioned. (Food and Drug Administration, 2018)
Lorbrena	No dose adjustment necessary in subjects with mild HI. No recommendations for moderate and severe. (Food and Drug Administration, 2018)
Lucemyra	Dose adjustment in HI described on the label. (Food and Drug Administration, 2018)
Lumoxiti	No dose adjustment necessary in subjects with mild HI. Not studied in subjects with moderate and severe HI. (Food and Drug Administration, 2018)
Lutathera	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Mektovi	No dose adjustment necessary in subjects with mild HI. Reduce dose for moderate and severe HI. (Food and Drug Administration, 2018)
Motegrity	No dose adjustment necessary. (Food and Drug Administration, 2018)
Moxidectin	The pharmacokinetics in HI was not studied. (Food and Drug Administration, 2018)
Mulpleta	No dose adjustment necessary for mild and moderate HI. Severe HI showed a decrease of C_{max} and AUC but provided no dose adjustment considerations. (Food and Drug Administration, 2018)
Nuzyra	No dose adjustment necessary. (Food and Drug Administration, 2018)
Olumiant	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Omegaven	Hepatic impairment was not mentioned. (Food and Drug Administration, 2018)
Onpattro	No dose adjustment necessary in subjects with mild HI. Moderate and severe HI were not studied. (Food and Drug Administration, 2018)
Orilissa	Dose adjustment in HI described on the label. (Food and Drug Administration, 2018)
Oxervate	Hepatic impairment was not mentioned. (Food and Drug Administration, 2018)
Palynziq	Hepatic impairment was not mentioned. (Food and Drug Administration, 2018)

Pifeltro	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Poteligeo	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Revcovi	Hepatic impairment was not mentioned. (Food and Drug Administration, 2018)
Seysara	No dose adjustment necessary in subjects with mild and moderate HI. Avoid in subjects with severe, for lack of studying. (Food and Drug Administration, 2018)
Symdeko	Dose adjustment in HI described on the label. (Food and Drug Administration, 2018)
Takhzyro	Hepatic impairment was not mentioned. (Food and Drug Administration, 2018)
Talzenna	No dose adjustment necessary in subjects with mild HI. Moderate and severe HI were not studied. (Food and Drug Administration, 2018)
Tavalisse	No dose adjustment necessary. (Food and Drug Administration, 2018)
Tegsedi	No dose adjustment necessary in subjects with mild HI. Moderate and severe HI were not studied. (Food and Drug Administration, 2018)
Tibsovo	No dose adjustment necessary in subjects with mild HI. Moderate and severe HI were not studied. (Food and Drug Administration, 2018)
Tpoxx	No dose adjustment necessary. (Food and Drug Administration, 2018)
Trogarzo	The pharmacokinetics in HI was not studied. (Food and Drug Administration, 2018)
Ultomiris	No dose adjustment necessary. (Food and Drug Administration, 2018)
Vitrakvi	No dose adjustment necessary in mild HI. 50% dose reduction recommended in subjects with moderate and severe HI. (Food and Drug Administration, 2018)
Vizimpro	No dose adjustment necessary in mild and moderate HI. No dosing recommendation established for severe HI. (Food and Drug Administration, 2018)
Xerava	No dose adjustment necessary for mild and moderate HI. Dose adjustment for severe HI is described on the label. (Food and Drug Administration, 2018)
Xofluza	No dose adjustment necessary in subjects with moderate HI. Severe HI was not studied. (Food and Drug Administration, 2018)
Xospata	No dose adjustment necessary in subjects with mild and moderate HI. Severe HI was not studied. (Food and Drug Administration, 2018)
Yupelri	Not recommended in patients with any degree of hepatic impairment. (Food and Drug Administration, 2018)
Zemdri	The pharmacokinetics in patients with hepatic impairment is unknown. (Food and Drug Administration, 2018)