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SAFE DRUG USE IN PATIENTS WITH CIRRHOSIS

Cirrhosis is the fibrosis of the liver as a result of different liver damage mechanisms that leads to the inflammation and generation of scar tissue, thus producing nodules. Liver cirrhosis affects both drug pharmacokinetics and pharmacodynamics, and must therefore be taken into consideration when prescribing. The severity and prognosis of cirrhosis are measured using the Child-Pugh classification.

The aim of this bulletin is to help with selection of the most appropriate therapeutic alternative for patients with cirrhosis by providing a series of safety and dose-adjustment guidelines for the drugs most commonly prescribed in primary healthcare.

When drafting these guidelines, we have based our recommendations on the corresponding summary of product characteristics, UpToDate® and the drug classification based on their safety in liver cirrhosis patients established by a committee of experts from the Netherlands by way of pharmacokinetic studies.

ANDREA RODRÍGUEZ ESQUÍROZ
Medicines Advice and Information Service
Navarre Health Service

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INTRODUCTION

The liver is the main metabolizer organ in the body and plays a key role in the elimination of numerous substances[1]. Cirrhosis is a chronic and progressive liver disease characterised by fibrosis, alterations of the liver architecture and the formation of regeneration nodules, which occasionally has functional consequences. In advanced stages of cirrhosis, this disease is irreversible[2]. Fibrotic liver diseases in which nodules do not form are not considered to be cirrhosis[1,2]. Liver cirrhosis affects drug metabolism and, as such, it is essential to take this disease into consideration when prescribing[3,4]. Liver failure is the inability of the liver to perform its normal physiological actions, such as the metabolism of endogenous and exogenous substances and the synthesis of plasma proteins[3,4].

Liver cirrhosis is characterised by fibrosis and the appearance of nodules in the liver

* *LIVER FAILURE IS A FUNCTIONAL ALTERATION OF THE LIVER, WHEREAS CIRRHOSIS IS A MORPHOLOGICAL ALTERATION OF THIS ORGAN. THERE MAY BE LIVER FAILURE WITH OR WITHOUT CIRRHOSIS AND CIRRHOSIS WITH OR WITHOUT LIVER FAILURE.*

There is currently no simple laboratory technique to determine liver function and its severity. Analytical tests do not correlate exactly with liver damage and may even be normal in patients with advanced liver disease. As such, they must be interpreted together with the patient's clinical presentation[2,5,6].

It is estimated that around 20% of drugs prescribed to patients with cirrhosis are incorrectly dosed or contraindicated and, as a result, 38% of patients suffer adverse drug reactions (ADRs), even though approximately 70% of them are preventable[7]. Although several studies concerning pharmacokinetic changes in liver cirrhosis have been published, as yet there is still no guideline with recommendation for the use and dosing of drugs in this situation[8-12]. Moreover, the summary of product characteristics for drugs often do not provide clear management and dosing recommendations, and these recommendations occasionally do not agree with the current safety data[13].

The aim of this bulletin is to help with selection of the most appropriate therapeutic alternative in liver cirrhosis and to provide a series of safety and dose-adjustment guidelines for the drugs most commonly prescribed in primary healthcare.

DIAGNOSIS AND SEVERITY OF CIRRHOSIS

There is currently no laboratory test to accurately diagnose liver cirrhosis, and imaging tests are required for its diagnosis. The severity and prognosis are measured using the Child-Pugh classification (Table 1), which gives a view of liver function[14].

Table 1. Child-Pugh classification for cirrhosis severity and prognosis.

Parameter	Score assigned to each parameter		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time Seconds over control or INR	 <4 <1.8	 4-6 1.8-2.3	 >6 >2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

The total score for the different parameters in the table gives an index, which indicates the degree of liver damage, with higher scores indicating greater severity:

- **5–6 points:** grade A: mild liver failure, well-compensated disease.
- **7–9 points:** grade B: moderate liver failure, with significant functional compromise.
- **10–15 points:** grade C: severe liver failure, decompensated disease[14].

A score of 8 or higher indicates deficient liver function, with potential decompensation and a high risk of complications and death. The Child-Pugh classification is not suitable for estimating the severity of other liver diseases in the absence of cirrhosis[14].

Patients with well-compensated cirrhosis (Child-Pugh A) do not typically present symptoms, although non-specific symptoms such as fatigue or reduced appetite may appear. The clinical manifestations normally appear in decompensated disease when complications such as ascites present. As such, this disease often goes unnoticed[1].

The Child-Pugh classification concerns the severity and prognosis of patients with cirrhosis and is not directly related to liver function

Changes to drug pharmacokinetics and pharmacodynamics occur in liver cirrhosis

HOW DOES CIRRHOSIS AFFECT PHARMACOKINETICS AND PHARMACODYNAMICS?

Absorption

The portal hypertension that appears during cirrhosis may result in the formation of collateral blood vessels in the liver and portosystemic shunts, thereby increasing the bioavailability of drugs with a high first-pass effect. This results in **elevated plasma concentrations** when these drugs are administered orally[8,15,16].

Distribution

The reduction of albumin and other plasma proteins production in patients with cirrhosis, together with the higher concentration of endogenous substances that attach themselves to the binding sites in albumin, such as bilirubin, causes an **increase in the free fraction** of those drugs that exhibit high protein binding. This, in turn, leads to an increase in the effect and/or toxicity, or accelerated elimination, depending on the drug. The presence of ascites may lead to **lower concentrations** of water-soluble drugs in systemic circulation as they are distributed into the ascitic fluid[3,8,15,16].

Metabolism

In cirrhosis there is a lower quantity of drug-metabolizing enzymes, although this is not proportional as the cirrhosis worsens and the different cytochromes are also not reduced in the same way[8,15,16]. Figure 1 shows the percentage activity of the main cytochromes involved in drug metabolism according to cirrhosis severity[17].

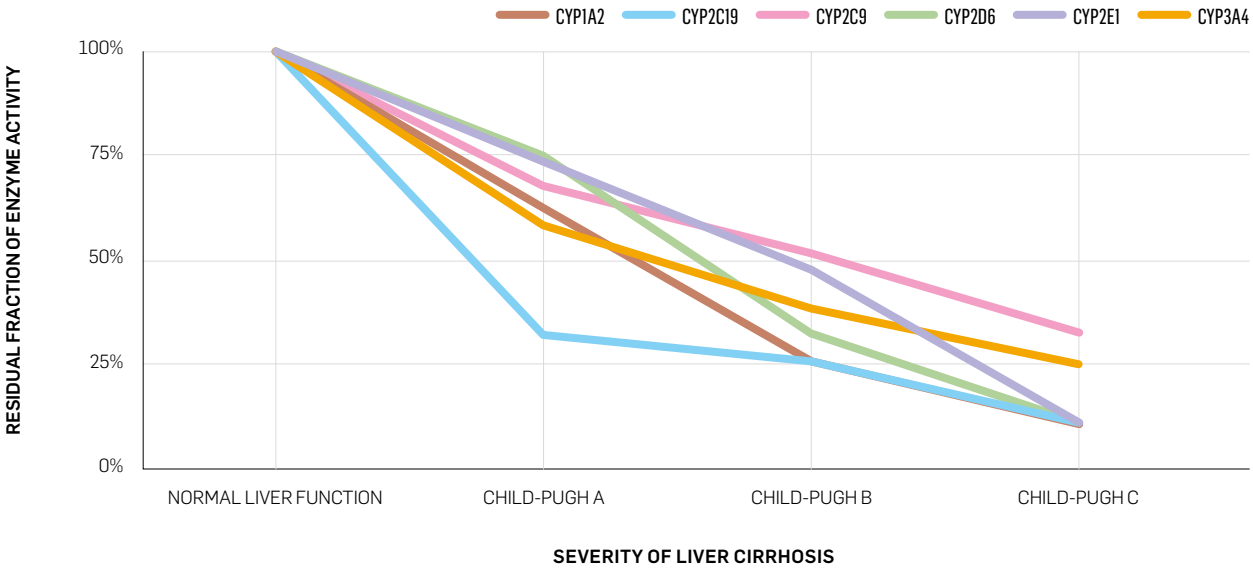
Excretion

The excretion of drugs eliminated via the bile duct is reduced, especially in patients with cholestasis. In most cases, this effect is compensated by the kidneys. As such, care must be taken with hepatorenal syndrome[8,15,16].

Pharmacodynamics

Patients with cirrhosis may present differences in the quantity and sensitivity of some receptors, thus altering the effect of some drugs, likediuretics, sedatives or anticoagulants. Moreover, these may be more susceptible to some ADRs, such as nephrotoxicity and clotting abnormalities[8,15,16].

Figure 1. Percentage of enzyme activity of the main cytochromes depending the severity of liver cirrhosis. Adapted from the data presented in Johnson et al.[17]



CAN I USE THIS DRUG IN LIVER PATIENTS WITH CIRRHOSIS?

The fact that a drug is hepatotoxic does not always mean that its use is contraindicated in patients with cirrhosis[18]. In such patients, the choice of drug and dose adjustment must be guided by the following factors:

- Indication for drug therapy: optimise the treatment and reduce the number of drugs.
- Pharmacokinetics of the drug.
- Safety of therapeutic alternatives.
- Comorbidities such as kidney failure, heart failure or alcoholism.
- Concomitant treatment and risk of drug interactions.
- Interactions with food and medicinal plants, such as grapefruit juice or St. John's wort.
- Severity of the cirrhosis, categorized using Child-Pugh classification.

Once treatment has been established, the onset of signs of decompensation of the cirrhosis and extrahepatic ADRs must be monitored. To that end, the participation of a multi-disciplinary team involving both primary and specialised care professionals is essential to perform dose adjustments and control the effect and tolerance of the treatment.

When preparing this bulletin, we relied on the classification provided by a committee of experts from the Netherlands and published by Weersink et al.[19], which classifies drugs into six groups on the basis of their safety profile, as based on pharmacokinetic studies in patients with hepatic cirrhosis (Table 2). The recommendations have been checked in the summary of product characteristics[20], UpToDate®[21] and the database on the Dutch version of the web page *Geneesmiddelen bij levercirrose*®[22]. The groups of drugs classified by the Dutch working group and marketed in Spain at the time this bulletin was drafted have been included. In case of the recommendations differ with the administration route used, the route is specified.

Data concerning the safety of drugs in liver patients with cirrhosis can be consulted at the following sources:

Geneesmiddelen bij levercirrose · RxCirrhose · UpToDate®

* *THE RECOMMENDATIONS IN THIS BULLETIN ARE LIMITED TO PATIENTS WITH ESTABLISHED LIVER CIRRHOSIS AND NOT TO OTHER LIVER DISEASES NOT ACCOMPANIED BY CIRRHOSIS.*

The drug-induced hepatotoxicity information can be consulted in:

cima · LiverTox livertox.nih.gov

Table 2. Classification of drugs based on their safety in patients with cirrhosis[19].

Classification	Description	Recommendation
Safe	Safety is supported by pharmacokinetic studies and/or long-term safety studies in these patients, with no safety problems having been found.	Can be used.
No risks known	The limited data suggest that the drug does not increase harm in comparison with patients with no cirrhosis. Drugs classified as "minimally affected by cirrhosis" (with hepatic clearance of less than 20%) based on their pharmacokinetics are included.	Can be used. Monitor adverse reactions. Dose adjustment may be required.
Risks known	The limited data suggest an increase in patient harm compared with patients with no cirrhosis. However, the number of studies is limited and/or the safety results are contradictory.	Do not use if a safer alternative is available. If used, possible adverse reactions must be monitored.
Unsafe	The data indicate that this drug is notsafe.	Avoid.
Unknown	Insufficient data evaluating the safety are available.	It should not be used if a safer alternative is available. Evaluate the risk/benefit for each patient.
Not classified	The safety has not been evaluated in patients with cirrhosis.	No recommendations can be made.

Analgesics (Table 3)

Non-steroidal anti-inflammatories (NSAIDs) must be avoided in patients with cirrhosis regardless of the severity due to the risk of kidney dysfunction and, as a result, decompensation of the cirrhosis. In addition, these patients are at higher risk of suffering gastrointestinal bleeding[22].

Hepatotoxicity does not always contraindicate drug use in patients with cirrhosis

Paracetamol is the analgesic of choice

Paracetamol is the analgesic treatment of choice. Although its metabolism is slowed in cirrhosis, the hepatotoxic metabolite (N-acetyl benzoquinone imine) does not increase and it can be used safely at non-hepatotoxic doses (up to 4 grammes per day). In patients with riskfactors for hepatotoxicity (such as malnutrition or alcohol consumption), the dose should be limited to 2 g per day[22]. There is currently insufficient evidence available concerning **metamizole**[20,22].

Gabapentin should be started at a low dose and slowly increased depending on the effect and tolerance. Caution must be exercised in patients with hepatic encephalopathy, impaired renal function and patients in concomitant treatment with other central nervous system depressants. Although there are currently no safety data available for **pregabalin** in cirrhosis, it is expected to be safe as hepatic metabolism is minimal[21].

The first-pass effect and metabolism of the majority of **opioid analgesics** is reduced in patients with cirrhosis, thus increasing the plasma concentrations. As such, the starting dose and/or dosing intervals should be adjusted and the dose should be increased gradually and more slowly than in patients without cirrhosis given the clinical effect and ADRs. Moreover, opioids have a greater risk of causing or worsening hepatic encephalopathy in these patients. Codeine and tramadol are prodrugs which are metabolised in the liver and converted into the active metabolite. As tramadol itself is also active, the dose should be adjusted[22]. Another source indicates that tramadol should not be used in Child-Pugh C for the treatment of chronic pain and should be stopped if a worsening of liver function is observed[21]. In the case of codeine, its conversion to morphine decreases markedly in advanced cirrhosis, therefore its use should be avoided[22].

Table 3. Safety and dose adjustment for analgesics in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
NON-OPIOIDS				
NSAID	Safety	Unsafe		
	Dose	Do not use		
Gabapentin	Safety[a]	No risks known		
	Dose	Standard	**Starting in patients with cirrhosis:** Start at ≤ 300 mg per day divided into 1–3 doses and increase depending on effect and tolerance **Adjustment if liver function worsens:** Standard	
Paracetamol ✔	Safety	Safe		
	Dose	Standard. In patients with hepatotoxicity risk factors: maximum dose 2 g/day		
OPIOIDS				
Buprenorphine	Safety	No risks known		
	Dose	Standard	Start with half the dose and increase gradually	
Codeine	Safety	Risks known	Unsafe	
	Dose	Standard	Do not use	
Fentanyl	Safety	Safe		No risks known
	Dose	Start with half the dose and increase gradually		
Hydromorphone	Safety	Unknown		
	Dose	Start with a quarter of the dose and increase gradually	No dosing recommendations	
Methadone	Safety	Risks known		
	Dose	Standard		
Morphine	Safety	No risks known		
	Dose (oral)	Start with half the dose and increase gradually		Start with a quarter of the dose and increase gradually
	Dose (IV)	No dose adjustment	Double the dosing interval	
Oxycodone	Safety	No risks known		
	Dose	Start with half the dose and increase gradually		Start with half the dose and double the interval
Tapentadol	Safety	Unknown		Unsafe
	Dose	Standard	Maximum starting dose 50 mg every 8 h (immediate release) or 50 mg every 24 h (prolonged release) and increase gradually	Do not use
Tramadol[b] ✔	Safety	No risks known		
	Dose	Start at 50 mg every 12 h and increase depending on effect and ADR[22]	Start at 25 mg and increase gradually. Maximum dose: 100 mg every 12 h[22]	
	Dose	**Starting in patients with cirrhosis:** ACUTE PAIN: Child-Pugh A: start at 50 mg every 8 h and increase to a maximum of 200 mg per day. Child-Pugh B: start at 25 mg every 8–12 h and increase to a maximum of 100 mg per day divided into 2–3 doses. Child-Pugh C: Do not use CHRONIC PAIN: Do not use **Maintenance after worsening of liver function:** Do not use[21]		

(a) The classification of gabapentin has been approved by the bulletin's editorial committee.
(b) Tramadol is the weak opioid of choice in cirrhosis.
(✔) Of choice.

Antidepressants (Table 4)

All selective **serotonin reuptake inhibitors (SSRIs)** are metabolised in the liver and their exposure increases with the severity of cirrhosis. Sertraline and fluoxetine are the most affected. In general, ADRs are dose-dependent, therefore it is recommended to start treatment at a low dose, increasing it gradually depending on the effect and tolerance[21,22].

The elimination of **venlafaxine** decreases as the severity of cirrhosis increases[22]. **Desvenlafaxine** is considered to be a safer alternative[21]. To date, the safety of other groups of antidepressants has not been evaluated[22].

Table 4. Safety and dose adjustment for antidepressants in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
Citalopram ✔	Safety	No risks known		
	Dose	Standard	Reduce by 50%	
Escitalopram ✔	Safety	No risks known		
	Dose	Start at 5 mg per day for two weeks then increase. Maximum dose 10 mg per day		
Fluoxetine	Safety	No risks known	Unsafe	
	Dose	Reduce by 50%	Do not use	
Fluvoxamine ✔	Safety	No risks known		
	Dose	Standard	Reduce by 50%	
Paroxetine	Safety	No risks known		Unsafe
	Dose	Standard	Reduce by 50%	Do not use
Sertraline	Safety	No risks known	Unsafe	
	Dose	Reduce by 50%, maximum dose 100 mg per day.	Do not use	
Venlafaxine	Safety	No risks known		Unsafe
	Dose	Reduce by 50%		Do not use
Desvenlafaxine	Safety	No risks known		
	Dose	Standard	Initial dose: 50 mg per day; maximum dose: 100 mg per day	

(a) The classification of desvenlafaxine has been approved by the bulletin's editorial committee.

(✔) Of choice.

Antidiabetics (Table 5)

The pharmacokinetics of **insulin** is not affected in patients with liver failure and there is a wide experience of its use in patients with cirrhosis[22].

Metformin can be used safely in Child-Pugh A and B cirrhosis provided the patient does not have other risk factors for lactic acidosis, such as alcohol consumption, dehydration, hypotension, kidney failure or heart failure. In Child-Pugh C metformin levels are considerably increased, therefore the dose should be reduced[22].

Table 5. Safety and dose adjustment for antidiabetics in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
INSULINS				
Insulin	Safety	Safe		
	Dose	Individual, depending on blood glucose levels and needs		
BIGUANIDES				
Metformin	Safety	Safe		Risks known
	Dose	Standard		Reduce by 50%
	Comments	Care should be taken in patients at risk of lactic acidosis		
SULFONYLUREAS				
Glibenclamide Gliclazide Glimepiride	Safety	No risks known		
	Dose	Start at the lowest possible dose and increase gradually depending on effect and tolerance		
MEGLITINIDES				
Repaglinide	Safety	Unknown	Risks known	
	Dose	Start at 50% of the dose and increase gradually depending on effect and tolerance	Start at 50% of the dose and increase gradually depending on effect and tolerance. Maximum dose: 4 mg a day	
THIAZOLIDINEDIONES				
Pioglitazone	Safety	No risks known		
	Dose	Start at 15 mg once daily and increase gradually. Maximum dose 45 mg per day		
iDPP4				
Alogliptin	Safety	No risks known		Unknown
	Dose	Standard		No dosing recommendations
Linagliptin	Safety	No risks known		
	Dose	Standard		
Saxagliptin	Safety	No risks known		
	Dose	Standard		
Sitagliptin	Safety	No risks known		Unknown
	Dose	Standard		No dosing recommendations
Vildagliptin	Safety	No risks known		
	Dose	Standard		
iSGLT2				
Canagliflozin	Safety	No risks known		Unknown
	Dose	Standard		No dosing recommendations
Dapagliflozin	Safety	No risks known		
	Dose	Standard		Start at 5 mg per day and then increase. Maximum dose: 10 mg a day
Empagliflozin	Safety	No risks known		
	Dose	Standard		

Sulfonylureas are metabolised in the liver and bind strongly to plasma proteins. However, extensive experience with their use in patients with cirrhosis confirms their safety[22]. The increased risk of hypoglycaemia with this group of drugs, especially in at-risk patients such as alcohol consumers, severe liver failure or kidney failure, should be taken into consideration.

As regards **meglitinides**, data are only available for repaglinide, the exposure of which increases with the severity of cirrhosis[22].

The limited data available regarding the use of **pioglitazone** in liver cirrhosis show that there are no differences in terms of exposure and adverse reactions in comparison with patients without cirrhosis[22].

With regard to **sodium-glucose cotransporter type 2 inhibitors (iSGLT2)**, there are few studies in cirrhosis, although they are well tolerated and it is unlikely that relevant pharmacokinetic changes occur[22]. The risk of urinary infections should be taken into consideration with this group of drugs as they have been associated with decompensation of cirrhosis[21]. To date, there are no safety data for ertugliflozin.

The pharmacokinetic studies published show minimal changes to the pharmacokinetics of **dipeptidyl peptidase 4 inhibitors (iDPP-4)** in liver cirrhosis, although little is known about their long-term safety[22].

There are currently no data available for **GLP-1 receptor analogues**.

Antihistamines (Tabla 6)

There are very few published studies regarding the pharmacokinetic changes of antihistamines in patients with cirrhosis. Except for ebastine and fexofenadine, the remainder are eliminated via the hepatic pathway and therefore their pharmacokinetics are affected. In a study in patients with severe liver cirrhosis, hydroxyzine induced hepatic encephalopathy[22].

Table 6. Safety and dose adjustment for antihistamines in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
Cetirizine Desloratadine Levocetirizine Loratadine	Safety	No risks known		
	Dose	Reduce by half		
Cinnarizine Ketotifen Rupatadine	Safety	Unknown		
	Dose	No dosing recommendations		
Ebastine Fexofenadine	Safety	No risks known		
	Dose	Standard		
Hydroxyzine Mizolastine	Safety	No risks known	Unknown	
	Dose	Standard	No dosing recommendations	

Antimicrobials (Table 7)

With regard to **penicillins**, there are published studies supporting the safety of amoxicillin and amoxicillin/clavulanic acid in liver cirrhosis. There are no published studies concerning the use of phenoxymethylpenicillin. Cases of neurological ADRs and anomalies in the blood count related to high penicillin doses have been reported in these patients[22]. To date, there are no data on the safety of **cephalosporins**, since they are mainly eliminated renally, liver cirrhosis is not expected to affect their pharmacokinetics[20,22].

Macrolides are mainly eliminated by the liver. However, the pharmacokinetics of azithromycin, clarithromycin and erythromycin are not significantly affected in cirrhosis. A study reported prolongation of the QT interval with the chronic use of erythromycin in patients with cirrhosis and transjugular intrahepatic portosystemic shunt, although not in patients with cirrhosis and with no shunt. Three studies analysed the safety of clarithromycin in the eradicative treatment of Helicobacter pylori in cirrhosis. The ADRs were mild and similar to those in patients without cirrhosis in all cases[22].

There are few data available regarding the use of oral **tetracyclins** in these patients, and their use should be avoided[19]. In the case of **quinolones**, several studies support the use of norfloxacin and ciprofloxacin but not levofloxacin[22].

Table 7. Safety and dose adjustment for antibiotics in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
PENICILLINS				
Amoxicillin ± clavulanic acid	Safety	Safe		
	Dose	Standard		
Phenoxymethylpenicillin	Safety	Unknown		
	Dose	No dosing recommendations		
MACROLIDES				
Azithromycin Clarithromycin Erythromycin	Safety	No risks known		
	Dose	Standard		
TETRACYCLINES				
Doxycycline Minocycline	Safety	Unknown		
	Dose	No dosing recommendations		
QUINOLONES				
Ciprofloxacin	Safety	Safe		
	Dose	Standard		
Levofloxacin	Safety	Unknown		
	Dose	Standard		
Moxifloxacin	Safety	No risks known		
	Dose	Standard		
Norfloxacin	Safety	Safe		
	Dose	Standard		
OTHER				
Trimethoprim/sulfamethoxazole	Safety	No risks known		
	Dose	Standard		
Fosfomycin (oral)	Safety	Safe		
	Dose	Standard		
Metronidazole	Safety	Risks known		
	Dose	Standard		Reduce by 50%
		Limit duration to 2 weeks		
Nitrofurantoin	Safety	Unknown		
	Dose	No dosing recommendations		

Although no studies of the pharmacokinetic changes with **fosfomycin** have been performed, it is not expected to cause problems in patients with cirrhosis when administered orally. No safety or dosing conclusion can be reached with the use of **nitrofurantoin**[22].

Metronidazole is extensively metabolised in the liver and its clearance is reduced in patients with cirrhosis, increasing the half-life and risk of accumulation. Long-term treatments increase the risk of encephalopathy, therefore treatment should be limited to a maximum of two weeks[22].

Various studies supporting the safety of **trimethoprim/sulfamethoxazole** in cirrhosis have not shown safety problems at low doses (maximum 160/800 mg once daily)[22].

Antipsychotics (Table 8)

There are very few published studies regarding the use of antipsychotics in patients with cirrhosis. These patients are more susceptible to the ADRs for these drugs, including extrapyramidal effects and sedation. The risk of onset or worsening of hepatic encephalopathy is also increased. When used, they should be started at the lowest possible dose and effectiveness and adverse reactions should be monitored; if possible, plasma levels should be measured[22].

Table 8. Safety and dose adjustment for antipsychotics in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
TYPICAL ANTIPSYCHOTICS				
Fluphenazine Flupentixol Perphenazine Periciazine Pimozide Tiapride Zuclopenthixol	Safety	Unknown		
	Dose	No dosing recommendations		
Haloperidol	Safety	No risks known		
	Dose	Start at 50% of the standard dose		Start at 25% of the standard dose
Sulpiride	Safety	No risks known		
	Dose	Start at the lowest standard dose		
ATYPICAL ANTIPSYCHOTICS				
Amisulpride Cariprazine Clozapine	Safety	Unknown		
	Dose	No dosing recommendations		
Aripiprazol	Safety	No risks known		Unknown
	Dose	Standard		No dosing recommendations
Lurasidone	Safety	Unknown		
	Dose	Standard	Start at 18.5 mg per day and then increase	
			Maximum dose: 74 mg per day	Maximum dose: 37 mg per day
Olanzapine	Safety	No risks known		Unknown
	Dose	Start at 5 mg per day and increase depending on effect and tolerance.		No dosing recommendations
Paliperidone	Safety	No risks known		Unknown
	Dose	Standard		No dosing recommendations
Quetiapine	Safety	No risks known	Unknown	
	Dose	Start at 25 mg per day and then increase 25–50 mg per day if required.	No dosing recommendations	
Risperidone	Safety	No risks known		Unknown
	Dose	Start at 0.5 mg twice daily, increasing by 0.5 mg each time if necessary.		No dosing recommendations

Antithrombotics (Table 9)

Haemostasis is altered in patients with cirrhosis, therefore anticoagulants must be used with caution. As the INR increases, determination of the aPTT is not reliable, thus making anticoagulant adjustment more difficult[22].

Direct oral anticoagulants (DOACs) do not increase the risk of haemorrhage in cases of mild or moderate cirrhosis compared with antivitamin K anticoagulants, heparins or patients without cirrhosis. No extended half-lives or increased exposure to apixaban, dabigatran or edoxaban have been observed in patients with Child-Pugh A or B. However, apixaban and edoxaban are metabolised by CYP enzymes, therefore a cirrhosis-related effect cannot be ruled out and they must be used with caution. In the case of rivaroxaban, exposure in Child-Pugh B patients increases two- to threefold, therefore other, safer alternatives must be selected. There is insufficient information regarding the use of DOACs in Child-Pugh C patients. There is no published information about the use of **fondaparinux**[22].

With regard to **antiaggregants**, the risk of bleeding and thrombosis must be evaluated on an individual basis. As acetylsalicylic acid is the antiaggregant with the widest use experience, it is the drug of choice. There are currently no data regarding the use of ticlopidine[22].

Table 9. Safety and dose adjustment for anticoagulants and antiaggregants in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
DIRECT ANTICOAGULANTS				
Apixaban	Safety	No risks known	Unknown	
	Dose	Standard	No dosing recommendations	
Dabigatran	Safety	No risks known		Unknown
	Dose	Standard		No dosing recommendations
Edoxaban	Safety	No risks known	Unknown	
	Dose	Standard	No dosing recommendations	
Rivaroxaban	Safety	No risks known	Unsafe	
	Dose	Standard	Do not use	
ANTIVITAMIN K ANTICOAGULANTS				
Acenocumarol	Safety	No risks known		
	Dose	Starting dose: 3–4 mg day 1, 2 mg day 2, 1 mg day 3 and monitor INR day 4		
LOW MOLECULAR WEIGHT HEPARINS				
Dalteparin Enoxaparin	Safety	No risks known		
	Dose	If used as treatment, dose twice daily instead of once daily.		
Tinzaparin	Safety	Unknown		
	Dose	No dosing recommendations		
PLATELET ANTIAGGREGANTS				
Acetylsalicylic acid ✔	Safety	No risks known		
	Dose	Do not adjust when used as antiaggregant.		
Clopidogrel	Safety	No risks known		Unsafe
	Dose	Standard		Do not use
Dipiridamol	Safety	No risks known	Known adverse effects	
	Dose	Standard		
Prasugrel	Safety	No risks known		Unknown
	Dose	Standard		No dosing recommendations
Ticagrelor	Safety	No risks known	Unknown	
	Dose	Standard	No dosing recommendations	

(✔) Of choice.

Benzodiazepines and related drugs (Table 10)

Benzodiazepines are metabolized by the liver and their clearance is reduced in cirrhosis. In addition, these drugs increase the risk of hepatic encephalopathy in these patients, especially if they have a history of this condition. As such, their use must be avoided as far as possible.

If their use is considered necessary, prioritise the use of lorazepam given its short half-life. It is recommended to start at the lowest possible dose and gradually increase it, closely monitoring ADRs, especially during chronic use[22].

Table 10. Safety and dose adjustment for benzodiazepines in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
Alprazolam	Safety	Risks known		
	Dose	Start at half the standard dose		No dosing recommendations
Bromazepam Clorazepate Flurazepam Loprazolam	Safety	Risks known		
	Dose	No dosing recommendations		
Brotizolam	Safety	Risks known		
	Dose	Start at the lowest available dose	Start at half the standard dose	
Chlordiazepoxide	Safety	Risks known		
	Dose	Start at 1/3 the standard dose		No dosing recommendations
Clobazam	Safety	Risks known		
	Dose	Start at the lowest available dose		
Diazepam	Safety	Risks known		
	Dose	Start at half the standard dose		
Lorazepam ✔	Safety	Risks known		
	Dose	Start at the lowest available dose		No dosing recommendations
Lormetazepam	Safety	Risks known		
	Dose	Start at half the standard dose		No dosing recommendations
Midazolam	Safety	Risks known		
	Dose	Start at the lowest available dose	Start at half the standard dose	
Zolpidem	Safety	Do not use		
	Dose	Do not use		
Zopiclone	Safety	Risks known		
	Dose	Start at the lowest available dose	Start at half the standard dose	No dosing recommendations

(✔) Of choice.

Systemic corticosteroids (Table 11)

Both prednisolone and prednisone can be used safely in liver cirrhosis. However, the use of prednisolone should be prioritised as conversion of the prodrug prednisone into prednisolone is reduced in these patients. Serious ADRs and a reduced efficacy have been observed for budesonide, therefore its use should be avoided and other therapeutic alternatives must be used[22].

Table 11. Safety and dose adjustment for systemic corticosteroids in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
Budesonide	Safety	Unsafe		
	Dose	Do not use		
Prednisolone ✔	Safety	Safe		
	Dose	Standard		
Prednisone	Safety	Safe		
	Dose	Standard		

(✔) Of choice.

Lipid-lowering agents (Table 12)

With the exception of atorvastatin, which has exhibited increased plasma levels and risk of rhabdomyolysis in patients with cirrhosis, the majority of **statins** can be used safely in Child-Pugh A and B even though they are metabolised in the liver. The strongest evidence of safety is with simvastatin[22]. Moreover, simvastatin has been related to clinical benefits such as a lower portal pressure and reduced risk of hepatocarcinoma, thus making it the statin of choice[21,22]. These drugs should be started at the lowest possible dose, with subsequent adjustments based on their effect and tolerance. There are insufficient published data in Child-Pugh C[22].

Simvastatin is the statin of choice

There are very few published studies regarding the pharmacokinetic changes of **fibrates** in cirrhosis, despite the fact they are metabolised in the liver. Gemfibrozil and bezafibrate were studied in a trial and no ADRs were found in Child-Pugh A, although the safety in more severe stages remains unknown. No studies have been performed with fenofibrate[22].

Exposure to **ezetimibe** increases with the severity of cirrhosis, and it is unsafe in advanced disease[22].

Table 12. Safety and dose adjustment for lipid-lowering drugs in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
STATINS				
Atorvastatin	Safety	Unsafe		
	Dose	Do not use		
Fluvastatin	Safety	No risks known		Unknown
	Dose	Start at 20 mg per day and then increase depending on effect and ADR		No dosing recommendations
Pravastatin	Safety	No risks known		Unknown
	Dose	Start at 10 mg per day and then increase depending on effect and ADR		No dosing recommendations
Rosuvastatin	Safety	No risks known		Unknown
	Dose[21]	Start at 5 mg per day and then increase depending on effect and ADR	Start at 5 mg per day and then increase depending on effect and ADR up to a maximum of 10 mg	Use another alternative; if considered necessary, maximum dose 5 mg
Simvastatin ✔	Safety	Safe		Unknown
	Dose	Start at 20 mg per day and then increase depending on effect and ADR	Start at 20 mg per day and then increase depending on effect and ADR. Maximum dose 40 mg.	Start at 20 mg per day and then increase depending on effect and ADR. Maximum dose 40 mg (20 mg if decompensated cirrhosis)
FIBRATES				
Bezafibrate	Safety	No risks known	Unknown	
	Dose	Standard	No dosing recommendations	
Fenofibrate	Safety	Unknown		
	Dose	No dosing recommendations		
Gemfibrozil	Safety	No risks known	Unknown	
	Dose	Standard	No dosing recommendations	
OTHER				
Ezetimibe	Safety	No risks known	Unsafe	
	Dose	Standard	Do not use	

(✔) Of choice.

Digestive therapy (Table 13)

There are no published studies regarding the pharmacokinetics and safety of **antacids** in patients with liver cirrhosis. However, given their low absorption and mainly renal elimination, their pharmacokinetics is expected to be relatively unaffected[22].

The pharmacokinetics of **histamine-2 (H2) receptor antagonists** is only slightly affected in Child-Pugh A and B patients[22].

The pharmacokinetics of **some proton-pump inhibitors (PPIs)** is markedly affected in patients with cirrhosis due to their extensive hepatic metabolism. The plasma concentrations of pantoprazole and lansoprazole increase between four- and sevenfold. In Child-Pugh C patients, esomeprazole is the only PPI that has been shown to be safe and is therefore the drug of choice. Omeprazole metabolism is affected by CYP2C10 polymorphisms, whereas esomeprazole metabolism is much less affected. In addition, it is important to ensure the indication for PPI treatment given the greater risk of spontaneous bacterial peritonitis and hepatic encephalopathy for these patients during use. Moreover, the risk of respiratory infections, bone fractures and hypomagnesaemia in long-term treatments with these drugs must be taken into consideration[22].

As regards **prokinetic** drugs, exposure to metoclopramide increases from Child-Pugh B. The plasma concentrations of domperidone increase threefold in Child-Pugh B and are expected to increase with disease severity, therefore this drug should be avoided[22].

Table 13. Safety and dose adjustment for digestive system drugs in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
ANTACIDS				
Magnesium/aluminium hydroxide Magnesium/calcium carbonate	Safety	Unknown		
	Dose	No dosing recommendations		
H2 ANTAGONISTS				
Famotidine	Safety	No risks known		
	Dose	Standard		
PROTON PUMP INHIBITORS				
Esomeprazole ✔	Safety	No risks known		
	Dose	Standard		Maximum 20 mg per day
Lansoprazole	Safety	Unsafe		
	Dose	Do not use		
Omeprazole	Safety	No risks known		Unsafe
	Dose	Maximum dose: 20 mg per day		Do not use
Pantoprazole	Safety	Unsafe		
	Dose	Do not use		
Rabeprazole	Safety	No risks known		Unsafe
	Dose	Start at 10 mg per day. Maximum dose: 20 mg per day	Maximum dose: 10 mg per day	Do not use
PROKINETIC AGENTS				
Domperidone	Safety	No risks known		Unsafe
	Dose	Standard	One third of the standard dose	Do not use
Metoclopramide ✔	Safety	No risks known		
	Dose	Standard	50% of the standard dose	

(✔) Of choice.

Cardiovascular therapy (Table 14)

ACE inhibitors and **ARA-IIs** may increase the risk of hypotension and renal impairment in Child-Pugh B and C patients. Its use is not recommended in patients with cirrhosis and ascites. If used, the initial dose must be as low as possible and blood pressure and kidney function must be closely monitored[22].

Calcium channel blockers are mainly eliminated by the liver and the pharmacokinetics are affected in patients with cirrhosis. Reduced doses are required in these patients, although this is not always possible as the commercial presentations available cannot be fractionated. Cases of cardiogenic shock have been reported in patients with cirrhosis receiving treatment with verapamil and diltiazem after insertion of a transjugular intrahepatic portosystemic shunt. The use of amlodipine, nifedipine and diltiazem should be prioritised as the pharmacokinetics of the former are affected to a lesser extent, adjusting the dose[22].

The pharmacokinetics of liposoluble **beta-blockers** is markedly affected in liver cirrhosis as they present an extensive first-pass effect and the plasma concentrations may increase. It is recommended to increase the dose gradually, depending on the effect and tolerance[22].

There is extensive experience with **furosemide** in liver cirrhosis, therefore it is a a safe option. However, ADRs, such as hypokalaemia, hyponatraemia, renal dysfunction, muscle cramps and the onset of hepatic encephalopathy, must be monitored, especially in the first weeks of treatment[22].

Spironolactone is the **potassium-sparing diuretic** most extensively used in cirrhosis. Exposure to triamterene markedly increases in these patients and cases of severe ADRs, such as megaloblastic anaemia, have been reported, therefore this drug should be avoided[22].

There are very few published data regarding **thiazide diuretics** and, if used, electrolyte changes must be monitored due to the risk of hepatic encephalopathy[22].

Table 14. Safety and dose adjustment for cardiovascular system drugs in patients with cirrhosis.

		CHILD-PUGH A	CHILD-PUGH B	CHILD-PUGH C
ACEI				
Benazepril Captopril Enalapril Fosinopril Lisinopril Perindopril Ramipril Quinapril	Safety	No risks known	Risks known	Unsafe
	Dose	Start at the lowest possible dose and increase gradually depending on effect and tolerance		Do not use
ARA-II				
Candesartan	Safety	No risks known	Risks known	Unsafe
	Dose	Start at 4 mg per day and then increase gradually		Do not use
Eprosartan Irbesartan	Safety	No risks known	Risks known	Unsafe
	Dose	Start at the lowest possible dose and increase gradually		Do not use
Losartan	Safety	No risks known	Risks known	Unsafe
	Dose	Start at 12.5 mg per day and then increase gradually		Do not use
Olmesartan	Safety	No risks known	Risks known	Unsafe
	Dose	Start at 10 mg per day and then increase gradually	Start at 10 mg per day and then increase gradually. Maximum dose 20 mg per day	Do not use
Telmisartan	Safety	No risks known	Risks known	Unsafe
	Dose	Start at 20 mg per day and then increase gradually. Maximum dose 40 mg per day		Do not use
Valsartan	Safety	No risks known	Risks known	Unsafe
	Dose	Start at half the dose and increase gradually. Maximum dose 80 mg per day		Do not use
CALCIUM CHANNEL BLOCKERS				
Amlodipine ✔	Safety	No risks known		
	Dose	Standard	Start at 2.5 mg per day	Start at 2.5 mg every other day
Barnidipine	Safety	Unsafe		
	Dose	Do not use		
Diltiazem ✔	Safety	No risks known		
	Dose	Start at half the dose and increase gradually depending on effect and ADR		
Felodipine	Safety	No risks known		Unsafe
	Dose	Start at 2.5 mg per day		Do not use
Lacidipine	Safety	Unknown		
	Dose	Start at 2 mg once per day		
Lercanidipine	Safety	Unknown		Unsafe
	Dose	No dosing recommendations		Do not use
Nicardipine (oral)	Safety	Unsafe		
	Dose	Do not use		
Nifedipine ✔	Safety	No risks known		
	Dose	Start at half the standard dose		Start at half the standard dose and double the dosing interval
Nimodipine (oral)	Safety	No risks known		
	Dose	Start at 30 mg three times per day		
Nitrendipine	Safety	Unsafe		
	Dose	Do not use		
Verapamil (oral)	Safety	No risks known		Unsafe
	Dose	Start at 40 mg twice per day and then increase depending on effect and ADR. Maximum interval every 12 hours		Do not use
NON-CARDIOSELECTIVE BETA-BLOCKERS				
Carvedilol ✔ (m)	Safety	Safe		
	Dose	Standard	Start at half the standard dose	Start at 25% of the standard dose
Labetalol (oral) (h)	Safety	No risks known		
	Dose	Start at half the standard dose		
Propranolol ✔ (l)	Safety	Safe		
	Dose	Maximum starting dose: 20 mg 3 times per day		
Sotalol (h)	Safety	No risks known		
	Dose	Standard		
CARDIOSELECTIVE BETA-BLOCKERS				
Atenolol ✔ (h)	Safety	Safe		
	Dose	Standard		
Bisoprolol (m)	Safety	No risks known		
	Dose	Start at 2.5 mg per day[21]		Start at 2.5 mg per day[21] Maximum dose 10 mg/day
Celiprolol (m)	Safety	Unknown		
	Dose	No dosing recommendations		
Esmolol (h)	Safety	No risks known		
	Dose	Standard		
Metoprolol (l)	Safety	No risks known		Unsafe
	Dose	Standard	Start at 1/3 the standard dose	Do not use
Nebivolol (m)	Safety	Unsafe		
	Dose	Do not use		
LOOP DIURETICS				
Bumetanide	Safety	No risks known		
	Dose	Standard		
Furosemide	Safety	Safe		
	Dose	Standard		
POTASSIUM-SPARING DIURETICS				
Amiloride Eplerenone	Safety	No risks known		
	Dose	Standard		
Spironolactone ✔	Safety	Safe		
	Dose	Standard		
Triamterene	Safety	Unsafe		
	Dose	Do not use		
THIAZIDE DIURETICS				
Chlortalidone Indapamide	Safety	Unknown		
	Dose	No dosing recommendations		
Hydrochlorothiazide	Safety	No risks known		
	Dose	Standard		

(h) Water-soluble. (m) Moderately liposoluble. (l) Liposoluble. The pharmacokinetics of liposoluble beta-blockers is markedly affected in liver cirrhosis as they present an extensive first-pass effect and their plasma concentrations may increase.

(✔) Of choice.

Conclusions

Cirrhosis affects drugs safety as a result of pharmacokinetics and pharmacodynamics changes, and the risk of adverse reactions may therefore increased. Consequently, this must be taken into consideration when prescribing.

In this regard, both prescription medications and over-the-counter drugs and alternative therapies (such as herbal products) that the patient is taking should be considered. It is important to educate patients with cirrhosis that they should consult a healthcare professional before taking any type of medication.

The safety of drugs in liver cirrhosis will depend on the severity of the disease, as estimated using the Child-Pugh classification. As such, it is important that this classification is available in the medical records so that it can be taken into account when prescribing medications.

The fact that a drug is hepatotoxic does not always mean that its use is contraindicated in patients with cirrhosis.

Having reviewed the literature, we can state that there are no data regarding the management of the majority of drugs in liver cirrhosis. Available recommendations are occasionally not in agreement in the different sources consulted.

Further studies in this field are therefore required to generate reliable and up-to-date data for the management of patients with liver cirrhosis in a safe way.

Annex 1
Drugs to be avoided in patients with cirrhosis

A series of drugs that must be avoided in patients with a diagnosis of liver cirrhosis, depending on its severity, and the safest therapeutic alternative, are listed below. It should be noted that the dose of therapeutic alternatives may need to be adjusted depending on the Child-Pugh classification[22].

Drug class	Avoid	Child-Pugh	Why is it unsafe?	Alternative
NSAID	All	A-C	Risk of kidney failure and decompensation	Paracetamol
Weak opioids	Codeine	C	Increased plasma levels	Tramadol
Beta-blockers	Nebivolol	A-C	Decreased first-pass effect	Propranolol Atenolol Carvedilol
	Metoprolol	C		
Calcium channel blockers	Barnidipine Nicardipine Felodipine Lercanidipine	A-C	Pharmacokinetic changes	Amlodipine Nifedipine Diltiazem
	Verapamil	C		
Diuretics	Triamterene	A-C	Increased exposure. Increased risk of megaloblastic anaemia.	Spironolactone
ACEI and ARA II	All	B-C	Risk of hypotension and kidney failure	
Cholesterol-lowering drugs	Atorvastatin	A-C	Increased plasma levels	Simvastatin
Antiplatelet agents	Dipyridamole	B-C	Risk of kidney failure	Acetylsalicylic acid
Proton pump inhibitors	Pantoprazole Lansoprazole	B-C	Increased plasma levels due to reduced clearance	Esomeprazole
Prokinetic agents	Domperidone	C	Increased plasma levels	Metoclopramide
Glucocorticoids	Budesonide	A-C	Increased exposure. Lower effect and more severe ADRs in patients with cirrhosis.	Prednisolone
Benzodiazepines and analogs	All, especially zolpidem	A-C	Risk of hepatic encephalopathy	Lorazepam
SSRI antidepressants	Fluoxetine Sertraline	B-C	Increased exposure. Increase in dose-dependent ADRs	Citalopram Escitalopram Fluvoxamine
	Paroxetine	C		
	Venlafaxine	C		Desvenlafaxine

Table adapted from Borgsteede et al[22] ADR: adverse drug reaction.

Annex 2
The situation in Navarre

In June 2023 there were 1326 patients with a diagnosis of liver cirrhosis in Navarre. Of these, 52 were classified as Child-Pugh A (3.9%), 63 as Child-Pugh B (4.8%), 23 as Child-Pugh C (1.7%) and the remainder (89.6%) had no classification in the computerised medical records.

Between April and June 2023, 431 active prescriptions of contraindicated medications in liver cirrhosis were detected in 335 (25.3%) patients. The medicines used are listed in Table 15. A safe therapeutic alternative was available in all cases. Medications contraindicated only in less severe forms of cirrhosis could not be evaluated as the Child-Pugh classification was not available.

Therapeutic group	Active substances	Number of prescriptions
Proton pump inhibitors	Pantoprazole	144 (33.4%)
	Lansoprazole	22 (5.1%)
	Total	**166 (38.5%)**
Lipid-lowering agents	Atorvastatin	131 (30.4%)
	Total	**131 (30.4%)**
Non-steroidal anti-inflammatory drugs	Ibuprofen	30 (7.0%)
	Dexketoprofen	21 (4.9%)
	Naproxen	11 (2.6%)
	Condroitin sulfate	8 (1.9%)
	Diclofenac	8 (1.9%)
	Etoricoxib	5 (1.2%)
	Celecoxib	5 (1.2%)
	Aceclofenac	3 (0.7%)
	Lornoxicam	1 (0.2%)
	Total	**83 (21.3%)**
Hypnotics	Zolpidem	32 (7.4%)
	Total	**32 (7.4%)**
Cardiac therapy	Nebivolol	4 (0.9%)
	Barnidipino	4 (0.9%)
	Nitrendipino	2 (0.5%)
	Total	**10 (2.3%)**

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Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
sinfomed@navarra.es

Web site
www.dtb.navarra.es