KCE REPORT 276CS

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUMMARY

TOWARDS AN EXPANSION OF THE REIMBURSEMENT CONDITIONS FOR HEPATITIS C THERAPIES?

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FOREWORD

The arrival of new antiviral drugs against hepatitis C virus is undoubtedly one of the most noteworthy medical breakthroughs of the recent years. In comparison to the therapies available up and until then, their efficacy is spectacular and - more importantly - their side effects are far less numerous. This is an incredible beacon of hope for the thousands of people who have been carrying the virus for years or even decades. But there is a downside: these therapies are also incredibly expensive such that, if we want to keep our system somewhat in balance, we find ourselves locked in a situation that is both surrealistic and cynical. Do we wait until patients have developed irreversible liver lesions before we decide to reimburse these medicines which, if they had been administered earlier, could have prevented the lesions?

Even if not everyone carrying the virus progresses to the most advanced stages of the disease, and even if the course of the disease is generally slow, we know that all those carrying the hepatitis C virus are, year after year, forced to live with the sword of Damocles hanging over their heads and with the fear of infecting their nearest and dearest. In these circumstances, it is painful having to “wait” for treatment, all the more so when one knows that an effective treatment is available.

The dizzying prices of these new antiviral agents have led to reconsider, not only here but also all over the world, the current business model of the pharmaceutical world. KCE and its Dutch counterpart, ZIN, recently embarked on a process of reflection on this issue but the alternative scenarios that have emerged basically deal with the mid to long term aspects while we want to start helping a maximum number of patients now.

In this report, we suggest a number of strategies to deal with this situation in the (very) short term. It is not up to the KCE to settle the matter but we hope that this document will shed light on the various options and will help the decision makers to answer this difficult question.

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Deputy General Director

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General Director

KEY MESSAGES

- There are no exact figures on the total number of people who have been infected with the hepatitis C virus in Belgium.
- The combinations of new-generation drugs, known as direct-acting antivirals (DAAs) show very high sustained virological response (SVR) rate. They are well tolerated and also allow for a reduction in the duration of the therapy (often to 12 weeks), which is a considerable improvement on the earlier therapies.
- Currently, only patients suffering from advanced fibrosis (score F3 or F4) and transplant patients (pre and post-transplantation) qualify for reimbursement of these new direct-acting antiviral therapies. This represents, in our country, a few hundred patients each year. Given the efficacy of these therapies, the question arises whether this target group should not be broadened.
- Traditionally, the fibrosis score was determined by means of a liver biopsy. Other non-invasive tests are now available (notably elastography and blood tests) but there are no robust data on the performance of a combination of these tests.
- This study looks into the cost and benefits of various possible strategies: no treatment, treating from F3 (the current situation), treating from F2 (on the basis of an elastography and blood tests of fibrosis), treating all patients whose blood tests only is positive and, lastly, treating everyone who carries the virus.
- Given that the damage caused by the virus is by and large irreversible, the quality of life of patients will especially improve if they are treated at an early stage.
- The economic evaluation shows that the more patients can be treated at an early stage (i.e. more we are inclusive), the more QALYs we gain at an additional cost of less than € 50,000/QALY.
- However, the option to treat every infected patient as early as possible before their condition has a chance to deteriorate is likely to take a heavy impact on the budget. For that reason, we suggest a progressive expansion of the DAA therapy reimbursement conditions.
- The scale of the budget impact of this gradual reimbursement is nevertheless difficult to predict because of the various uncertainties that prevail, such as the number and profile of patients who are currently infected and not yet treated.
- A quarterly monitoring of the number of patients treated and, where appropriate, an urgent renegotiation of the prices and reimbursement criteria are required if we want to prevent a budget explosion. Furthermore, any expansion of the eligible population must go hand in hand with an additional reduction in the cost of these therapies to ensure that the entire healthcare system is not put in jeopardy.
- To obtain a more significant price reduction, which would allow reimbursements to be broadened faster, other options could be explored, such as joint procurement agreements with other countries to purchase these medicines.

- In Belgium, and internationally, the hepatitis C virus is more prevalent among high-risk groups, mainly intravenous drug users. This compromises all the forecasts as to the eradication of the virus. For these populations, significant outreaching efforts, support and harm reduction programmes are required.

SUMMARY

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1. BACKGROUND

1.1. Hepatitis C

The hepatitis C virus (HCV) was discovered in 1989. From that moment, the condition previously labelled as “non-A, non-B hepatitis” became known as hepatitis C.

HCV is mainly transmitted **through blood** (see the frame below). In some people, the virus disappears spontaneously but in 75 % to 80 % of cases, the infection becomes a chronic condition. It can remain asymptomatic for decades, yet slowly but surely lead to liver fibrosis, then **compensated cirrhosis**, and possibly **cancer (hepatocellular carcinoma)** or **decompensated cirrhosis**. These two complications are fatal within a relatively short period of time; the only way to treat them is by means of a liver transplant.

It is estimated that, in Belgium, 40 % of terminal cirrhosis cases are caused by the hepatitis C virus. Furthermore, according to data from the HepCar Registry (2003), of the 131 new hepatocellular carcinoma diagnoses made in Belgium that year, 41% were caused by the hepatitis C virus, as against 17 % by the hepatitis B virus, 30 % by the consumption of alcohol and 12 % by various causes.

The fact that the infection clears up - spontaneously or as a result of therapy - is no guarantee for immunity. In other words, HCV patients can be reinfected again.

During the years of asymptomatic carriage, patients can also transmit the virus.

Routes of transmission

HCV is mainly transmitted through blood. Until 1990, the year the systematic screening of blood donors was introduced, blood transfusions and organ transplants were the main source of infection (mainly genotype 1). Thanks to the precautionary measures taken in relation to blood donations, this route of transmission has been eliminated in Belgium.

Since then, the majority of new infections (80 % to 90 %) in the Western world are found in injection/intravenous drug users (IDUs), who transmit the virus by sharing needles and other drug injection paraphernalia. Overall, it is estimated that at least 50 % of the IDU population in Western Europe is chronically infected with VHC. Another less frequent route of infection is intranasal transmission using contaminated drug sniffing implements such as straws, used to snort cocaine, heroin, and other powdered drugs.

Sexual transmission occurs most frequently in immunodeficiency virus (HIV) positive gay and bisexual men, especially after contracted clinical syphilis and/or lymphogranuloma venereum rectitis.

Other, more marginal, routes of transmission include tattooing, medical procedures and mother-to-baby transmission at birth.

Lastly, new HCV infections have also been detected in first-generation migrants from countries with a strong prevalence of HCV, although statistics allowing to assess the extent of the problem are scarce.

1.2. Number of HCV-infected people in Belgium

There is few data on the epidemiology of hepatitis C in our country. Old figures (1994) assessed HCV seroprevalence (presence of HCV antibodies in the blood) in the population of Flanders at 0.87 %-1 %, which, extrapolated to Belgium, translated into between 93,000 and 107,000 individuals at the time (of which half were unaware that they were carriers). Another study from 2007 estimated seroprevalence at 0.12 %, which corresponds to some 12,500 individuals.

Very recently (2015), the Scientific Institute of Public Health estimated the incidence of HCV at some 1500 new cases per year (13.6 per 100,000 inhabitants a year).

International seroprevalence data suggest that hepatitis C is currently more prevalent in certain **risk groups**, but there are very few Belgian data on these populations:

- Concerning **intravenous drug users** (IDUs), the most recent data (2011) report a 55 % seroprevalence among IDUs, but these figures are based on heterogeneous data and fairly limited groups, which means that they should be used with caution.
- In 2006, the prevalence of hepatitis C antibodies in Belgian prisons has been estimated at 7.5 %. About 76% of imprisoned drug injectors seeking healthcare were tested positive for anti-HCV antibodies according to a 2005 Belgian report.
- Another risk group which has been identified in the past 15 years is the population of men who have sex with men (MSM). The annual incidence of HCV infection among HIV-positive MSM has risen from 0.2% in 2001 to 1.51% in 2008, peaking at 2.9 % in 2009. Often, it is associated with other sexually transmitted diseases.
- Lastly, new HCV infections have also been detected in first-generation migrants from countries with a marked prevalence of HCV.

1.3. Therapies

There is **no preventive vaccine** against hepatitis C.

For many years, the standard treatment for chronic hepatitis C was based on broad-spectrum antiviral injections of **interferon alpha** (IFNα), then on long-acting formulas (PegIFN) combined with oral courses of **ribavirin** (RBV). The efficacy of these therapies is measured in terms of **sustained virologic response** (SVR) rate, which means that the RNA of the virus remains undetectable in the blood for 12 or 24 weeks after the end of the treatment. It is worth noting however that even following SVR, the virus can still resurface in a small percentage of patients.

The efficacy of interferon-based therapies was variable however and notably depended on the virus's genotype. To illustrate, SVR was obtained in up to 80 % of genotype 2 and 3 infections after a 6-month therapy with PegIFN in combination with RBV, while, in genotype 1 infections, a 12-month therapy only resulted in a SVR rate of about 45% (KCE report 173). What's more, the considerable side effects (fatigue, depression) of these drugs, in addition to the symptoms caused by the illness itself, often made for poor patient compliance. Also the list of contraindications was fairly daunting.

In the last few years, a new generation of antiviral agents has become available, offering treatment options without interferon, and sometimes without ribavirin even. These drugs, known as **"direct-acting antivirals" (DAAs)** are far more effective than the earlier treatments, regardless of the genotype. When combined, they can result in an SVR of 95 %, or more. At that, they come with far fewer side effects and contraindications. Lastly, they allow the duration of the therapy to be reduced, often to 12 weeks. Yet, all these advantages are undeniably outweighed by their very high price (about € 40 000 for non-cirrhotic patients). Thus, for budgetary reasons, these treatments are currently (since 2015) only reimbursed for patients in an advanced stage of the illness (F3 or F4 score of fibrosis - see section 2.2) and transplanted patients (pre and post-transplantation). In our country alone, we are talking about a few hundred patients each year.

1.4. Objectives of this report

The question that arises now is the following: **given the efficacy, the tolerance and the safety of these new therapies, would it not be right to extend reimbursement to patients in a less advanced stage of the disease, or to anyone who has been infected with the virus?** However, given the high cost of these therapies, such an expansion could put the health insurance budget at risk (other European countries are faced with the same problem).

In that light, the categories of patients likely to benefit most from the therapy, in terms of cost and efficacy, need to be identified and the budget impact of such an expansion of the reimbursement criteria assessed.

That is the aim of the present report, produced at the request of the National Institute for Health and Disability Insurance (RIZIV-INAMI).

We emphasise however that, by phrasing our research question in this manner, we postulate that only the new DAA-based therapies, without interferon, are envisaged. The decision not to include interferon-based products was taken in consultation with Belgian experts and RIZIV-INAMI, mainly in view of their numerous side effects.

2. ELIGIBILITY CRITERIA FOR THE TREATMENT

2.1. The current situation

The DAAs available in Belgium at the time this report was written are sofosbuvir (Sovaldi®, Gilead), sofosbuvir in combination with ledipasvir (Harvoni®, Gilead), a combination of ombitasvir, paritaprevir and ritonavir (Viekirax®, Abbvie), dasabuvir (Exviera®, Abbvie), daclatasvir (Daklinza®, Bristol-Myers Squibb) and simeprevir (Olysio®, Janssen-Cilag). “Temporary reimbursement conventions” for these pharmaceuticals have been signed with RIZIV-INAMI. These conventions set out the reimbursement terms and define the confidential price-volume agreements. So, the actual price of these drugs is unknown.

Currently, reimbursement of these pharmaceuticals is restricted to patients suffering from chronic hepatitis C with stage F3 or F4 of fibrosis and to pre- or post-transplanted patients. Only university hospitals are authorized to prescribe these therapies.

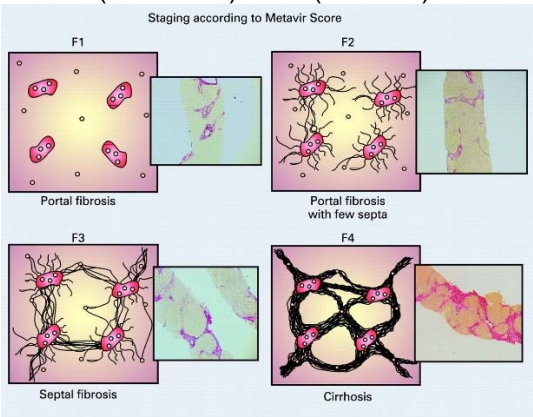
The conventions in question ran out in the summer of 2016. They are currently being reviewed and a possible expansion of the target group is being discussed.

2.2. Determining the stage of fibrosis through non-invasive tests?

Up to very recently, the usual examination to establish the degree of hepatic fibrosis was a histopathological (microscopic) examination of a liver sample taken by means of a **liver biopsy**. The result of a biopsy is expressed on the basis of a scoring system known as the METAVIR score which qualifies the degree of liver fibrosis in function of the histologic characteristics (F score) and the degree of inflammatory activity (A score) observed in the sample.

The METAVIR F score

The stages of fibroses based on the METAVIR score range from F0 (no fibrosis) to F4 (cirrhosis)



http://gut.bmj.com/content/58/6/846/F6.large.jpg
http://www.pathologyoutlines.com/topic/liverchronichepgrading.html

But a liver biopsy is an invasive test which carries a significant risk, notably haemorrhagic, especially in patients in an advanced stage of the illness.

These days, there are also a number of **non-invasive tests**. However, (so far) there are no studies that measure the long-term outcome of patients in function of the results of these non-invasive tests (the longest study ran over a 9-year period but was conducted on a relatively small sample). The only studies available are transversal studies which evaluate the sensitivity and specificity of these non-invasive tests in comparison with biopsies.

We have limited ourselves to the non-invasive tests commonly used in Belgium, i.e.:

- Elastography: the principle of this examination is to measure the elasticity of the hepatic tissue by means of an ultrasound probe which measures the propagation of an acoustic wave sent through the liver. The faster the wave travels, the harder the environment and the more serious the fibrosis. This method is non-invasive, painless and reproducible. Various variants of the technique are available (Fibroscan, ShearWave, ARFI). Yet, experts claim that the interpretation of the results of an elastography is rather subjective.
- Blood tests for fibrosis that combine the doses of various hepatic function markers on the basis of algorithms, characteristic of fibrosis (score FIB-4, Fibrotest). Experts consider this type of test to be more objective.

2.3. Setting the eligibility criteria

The choice of eligibility criteria for the reimbursement of these treatments was based on the proposal of Belgian experts from the “Hepatitis C” Working Group of the RIZIV-INAMI Drug Reimbursement Committee, i.e. the use of a **combination of an elastography and blood tests for fibrosis**. Where the results of both these tests exceeded the values hereafter, the firbosis stage were deemed to be equal to or above a METAVIR score of F2.

- Elastography: Fibroscan ≥ 7.2 kPa or ShearWave ≥ 7.1 kPa or ARFI ≥ 1.32 m/s
- Blood tests: FIB-4 > 1.45 or Fibrotest ≥ 0.49

However, two major uncertainties difficult to quantify remain:

1. We know the sensitivity and specificity of the tests individually but not of a combination of these tests. To be precise, we do not know the degree of **conditional dependency**, i.e. the probability that a false positive or false negative in one of these two tests also produces a false negative or false positive in the other test.

Thus, in relation to reimbursement strategy 2 (see below), which is based on a combination of tests,we propose **two scenarios**:

- A “sensitive” scenario (the combination of tests results in a 90 % sensitivity and a 90 % specificity rate): all the false negatives and false positives from one test will also produce false negatives and false positives in the other test;
- A “specific” scenario (the combination of tests results in a 80 % sensitivity and a 95 % specificity rate): conditional independence, with a loss in terms of sensitivity but a gain in terms of specificity.

2. We have no information on **conditional dependence in the case of repeat tests**. What are the chances of a patient being identified as being eligible for treatment if he was a false negative a year earlier? And what are the chances of a genuine negative becoming a false positive the following year? In our model, we assumed a conditional independence between repeated tests, but we cannot be certain.

That factor casts doubt over our prediction as regards the short-term effects (within 2 to 4 years) of any given test; it is crucial therefore to come up with a flexible reimbursement mechanism that can be adjusted ‘along the way’.

3. COST-EFFECTIVENESS ANALYSIS OF THE VARIOUS POTENTIAL STRATEGIES

3.1. Five strategies

We present five strategies to reimburse the treatment for patients suffering from HCV, defined on the basis of the proposals of the RIZIV-INAMI “Hepatitis C” Working Group.

- **Strategy 0: “no treatment”:** patients are neither tested nor treated. This strategy is a purely hypothetical one but serves as basis to calculate the budget impact.
- **Strategy 1 “treatment from F3” (= the previous practice in Belgium):** all the patients diagnosed with chronic hepatitis C undergo a biopsy and those with a fibrosis score ≥F3 are treated. Patients with a fibrosis score of less than F3 are retested each year until they become eligible for treatment.
- **Strategy 2 “treatment from F2 on the basis of an elastography and non-invasive blood tests for fibrosis (e.g. FIB-4)”:** all the patients diagnosed as suffering from chronic hepatitis C are assessed on the basis of a combination of two non-invasive tests (for a more detailed description, see the scientific report) and those where the two tests exceed the threshold values are deemed to have a fibrosis score ≥F2 and are treated. The other patients are retested each year until they become eligible for the treatment.
- **Strategy 3 “treatment on the basis of non-invasive blood tests, positive for hepatic fibrosis”:** all patients diagnosed with chronic hepatitis C are assessed by means of non-invasive blood tests (FIB-4) and those who turn out to be positive are treated. The other patients are retested each year until they become eligible for the treatment.
- **Strategy 4 “treating all patients”:** all patients who are diagnosed as being chronically infected with the hepatitis C virus (F0-F4) are treated.

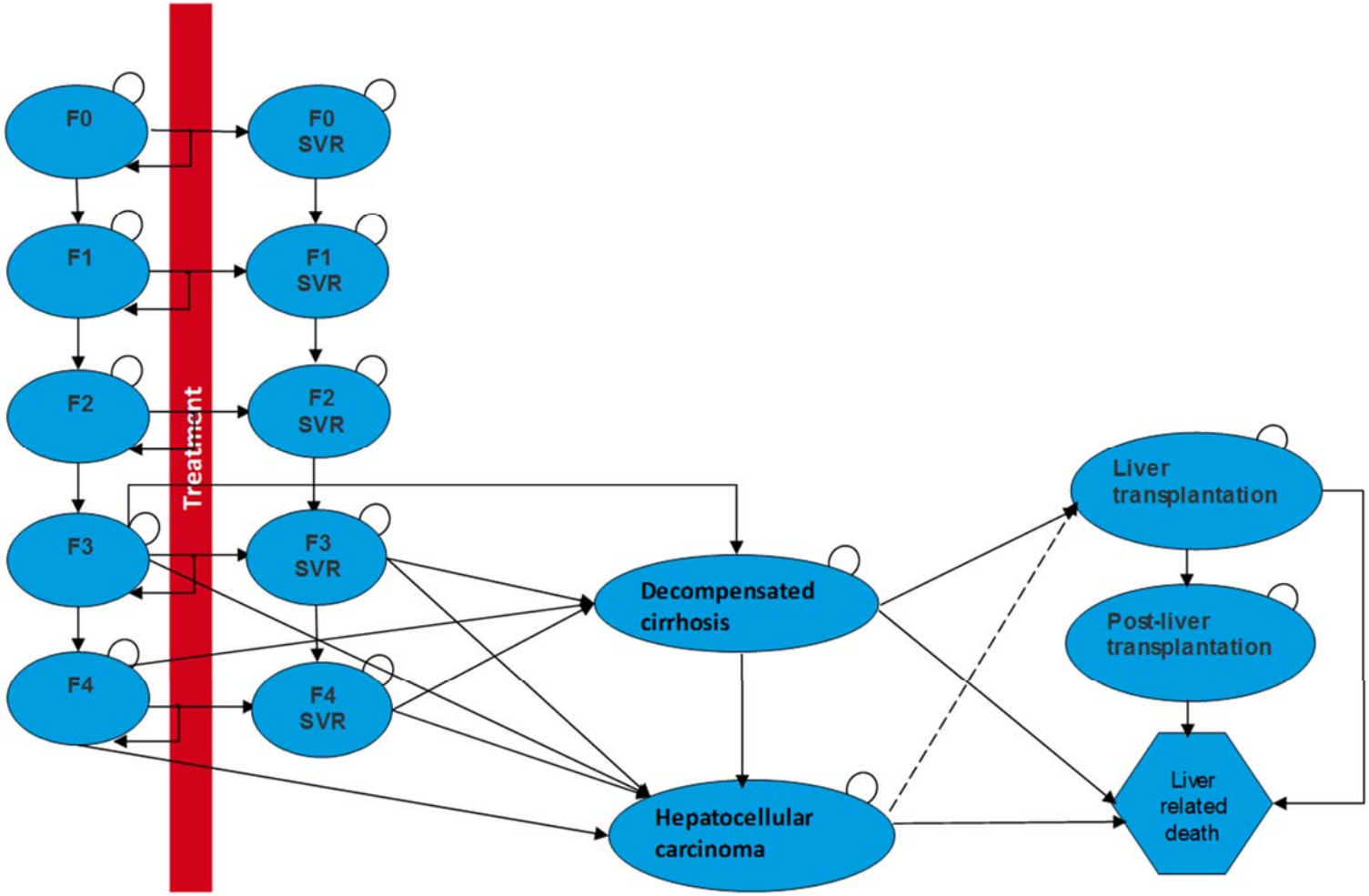
3.2. Method

For each of these scenarios, we conducted a **cost-effectiveness analysis** (calculating the additional cost for each life year gained) and a **cost-utility analysis** (calculating the additional cost for each quality-adjusted life-year gained, i.e. for each year in perfect health). To do so, we contructed a Markov model in Excel. This technique allowed us to model the evolution of a cohort of patients over time. It supposes that each patient is invariably in one of the states defined in the model – called "the Markov states", representing patients' various potential evolutions (see Figure 1). Based on an annual transition probability, each one of these states was then linked to the next state, and to a cost and a "utility" (allowing the assessment of the impact on the quality of life). The analyses were performed in line with the Belgian guidelines on economic evaluations and budget impact analyses (KCE Report 183), the main elements of which have been summarised in the frame below (next page).

As shown Figure 1, we considered that, even after SVR was obtained, the illness could continue to evolve in some patients but that this probability was lower than in non-SVR patients. The details of the parameters used (transition probabilities, costs and utilities), including our hypotheses, can be consulted in the scientific report.

It must also be emphasised that we have absolutely no idea about one of the model's crucial parameters, i.e. the cost of DAA therapy (as the conventions for these pharmaceuticals are confidential) and that we had to base ourselves on assumptions. Thus, we presumed a therapy cost of €40 000 for non-cirrhotic patients in the baseline analysis and then varied this cost from €17 500 to €70 000 in the uncertainty analysis (see the scientific report for further details).

Figure 1 – Description of the Markov model used in the economic evaluation



** As specified in the scientific report, for patients diagnosed with hepatocellular carcinoma, we only have one overall HCC-related death probability (including mortality after transplantation). The number of patients diagnosed with a carcinoma who received a transplant (dotted arrow) has therefore only been included to calculate the cost of managing these patients. An all-cause mortality has also been applied to the various states (= loops in the figure).*

Principal methodological elements of the analyses performed:

- **Perspective of the evaluation:** the cost-effectiveness analysis was conducted from the healthcare payers perspective and merely include the direct healthcare costs, i.e. official reimbursements by RIZIV-INAMI and the official part paid by patients. The budget impact analysis neverteless only takes the RIZIV-INAMI reimbursements into account.
- **Target population:** patients suffering from chronic hepatitis C, classified by individual fibrosis score (F0-F4). The starting age of the patients in our model is 45 years, which is considered to correspond to the average age of the patients diagnosed. We did not perform any analyses on specific populations such as intravenous drug users (IDUs) (see KCE report for IDU-specific analyses).
- **Time window**: the patients lifetime.
- **Discount rate:** 3% for future costs and 1.5% for future benefits (0% in the budget impact analysis).
- **Year of cost valuation:** 2015 (in € for Belgium).

3.3. Result of the cost-effectiveness and cost-utility analyses

Tables 1 and 2 show that, the broader the criteria, the greater the number of patients who can be treated at an early stage and the greater the gain in life years (LY) and quality-adjusted life years (QALY). In strategy 4, the additional cost does exceed €100 000 per life year gained however. On the other hand, when taking the impact on the quality of life into account, that cost stands at €12 362 per QALY. Thus, this shows the importance of the values used in the model to assess the impact of treatment on patients' quality of life and more specifically on the loss of quality of life in the advanced stages of the illness and how the quality of life improves in fibrosis stages F0-F4 once SVR is obtained. Given the few studies that have been conducted on this topic, it would be wise to link the reimbursement of these pharmaceuticals to the collection of data on the quality of life pre and post SVR.

It is worth noting here that the studies that are available on this topic did not assess the impact on the quality of life of asymptomatic patients, chronic carriers of the virus and unaware of it. As it can be presumed that an improvement in the quality of life of these patients following SVR will be rather limited, the results presented here cannot be extrapolated to a situation of mass screening of the population where the ICER is likely to be far less favourable.

Table1 – Cost-effectiveness analysis of the various strategies for 1000 patients (cost per life year gained - LY), at a therapy cost of € 40 000 (non-cirrhotic patients)

	Life years	Incremental life years	Cost	Incremental cost	Incremental cost per life year gained (ICER)
Strategy 0: No treatment	23 749.60	-	€54 823 613.18	-	-
Strategy 1: Treatment from F3	26 942.94	3 193.34	€55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treatment from "F2" (blood tests + elastography)	27 159.82	216.88	€56 893 082.83	€1 331 300.62	€6 138.47
Strategy 3: Treatment if the blood tests are positive	27 177.64	17.82	€57 206 824.13	€313 741.29	€17 606.97
Strategy 4: Treating all patients	27 189.32	11.68	€58 699 753.74	€1 492 929.61	€127 845.66

ICER: incremental cost-effectiveness ratio.

Table2 – Cost-utility analysis of the various strategies for 1000 patients (cost per quality-adjusted life year - QALY), at a therapy cost of € 40 000 (non-cirrhotic patients)

	QALYs	Incremental QALYs	Cost	Incremental cost	Incremental cost per QALY gained (ICER)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treatment from F3	23 616.35	4 246.36	€55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treatment from "F2" (blood tests + elastography)	24 290.64	674.29	€56 893 082.83	€1 331 300.62	€1 974.38
Strategy 3: Treatment if the blood tests are positive	24 379.14	88.50	€57 206 824.13	€313 741.29	€3 545.05
Strategy 4: Treating all patients	24 499.91	120.77	€58 699 753.74	€1 492 929.61	€12 362.23

ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life years.

3.4. Treatment of the uncertainty

To analyse the uncertainty surrounding our parameters, we tested various scenarios on the basis of the range of the possible values for each uncertain parameter (possible/realistic minimum and maximum values). The analysis has shown that our above conclusions are valid in the majority of the scenarios investigated, i.e., the broader the criteria - and, hence, the earlier the treatment - the greater the number of quality-adjusted life years gained, at an additional cost per QALY of less than €50 000, and, in the majority of cases, of less than €20 000 even (see the scientific report for further details).

However, the results will by and large depend on the price of the DAA therapy concerned. As specified above, the net price, after discounts, is unknown. Various, purely hypothetical, situations have therefore been analysed: €17 500, €35 000, €40 000 and €70 000 for non-cirrhotic patients (<F4) and €21 000, €42 000, €63 000 and €84 000 from stage F4. The analysis of the uncertainty around the price of the therapies notably brought to light that, when using our lowest price assumptions (i.e. €17 500 for non-cirrhotic patients and €21 000 from stage F4), a direct broadening of the criteria based on blood tests only (strategy 3) would be preferable from a cost-effectiveness point of view, because strategies 1 and 2 would be dominated by this strategy 3. What's more, even if the maximum values are tested (i.e. €70 000), the additional cost per QALY of the various strategies is still less than €26 000. Conversely, the impact on the budget is and remains considerable (see below).

The ranking between these different strategies also depends on the assumed performance of the tests used: the sensitivity and specificity of the individual tests and of the combined tests.

The ranking between strategies 1 to 3 can also vary if one assumes that the impact of the therapy (i.e. mainly the SVR rate and the probability of progression following SVR) differs in function of the stage of the patient's fibrosis. For instance, if one supposes that treatment is less effective from fibrosis stage F3 (a lower SVR rate than in stages F0-F2 or a more significant progression probability following SVR), the strategy of "treating patients from stage F3" will be dominated by an earlier treatment from stage F2. However, the differences in the impact of the treatment in function of the stage of the patient's fibrosis have as yet not been well documented in the literature and are purely hypothetical.

Lastly, the ICER value is linked to the estimated probabilities of the illness's progression and to the cost of the overall medical management.

We deliberately chose not to perform a probabilistic analysis but to focus on a multivariate scenario analysis instead, with a realistic "best case" scenario (retaining, from the range of potential values, the values that favoured treating the population at an early stage of the illness most) and a realistic "worst case" scenario (retaining, from the range of potential values, the values that favoured treating the population at an early stage of the illness least).

This analysis has shown that, in the best-case scenario, strategy 4 ("treating all patients") dominates all the other strategies. In the worst-case scenario, the additional cost of the various strategies is still less than € 50 000 per QALY (see table 4). It should also be noted that there is an extended dominance for strategy 2 ("treatment from F2 on the basis of an elastography and blood tests"), which means that it might be preferable to directly treat patients who were tested positive for the virus at the blood test of fibrosis, without performing an elastography. Yet, this will very much depend on the performance of these combined tests, which is completely uncertain. Thus, the performance of the combination of blood tests and elastography will need to be assessed and the choice of target population will need to be adjusted in function of the results obtained.

Why we decided not to conduct a probabilistic analysis

Even though the Belgian guidelines for economic evaluations recommend performing a probabilistic sensitivity analysis to address the uncertainty of the various parameters, an analysis like this can only be performed correctly if the uncertainty surrounding these parameters is known and sufficiently documented. Unfortunately, that is not the case here. Even if this uncertainty was available for a number of parameters, we are completely in the dark as regards a number of the model's other crucial parameters, more specifically those linked to the natural history of the illness, the effect of the treatment after SVR and the performance of the combined tests used to determine patient eligibility. By presenting a probabilistic analysis, the readers may have been led to believe that these results were solid and based on properly documented data.

Table 3 – "Best case" analysis

	QALYs	Cost	Incremental cost per QALY gained (ICER)
Strategy 0: No treatment	16 731.67	€83 130 203.11	Dominated strategy*
Strategy 1: Treatment from stage F3	23 378.20	€44 905 583.33	Dominated strategy*
Strategy 2: Treatment from stage "F2" (blood tests + elastography)	24 777.62	€41 301 076.33	Dominated strategy*
Strategy 3: Treatment if the blood tests for fibrosis are positive	25 653.43	€41 035 814.07	Dominated strategy*
Strategy 4: Treating all patients	26 018.92	€41 009 482.38	-

*A dominated strategy is a strategy that makes no sense because it costs more and is less effective than the one it is compared to.
ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life years.

Table 4 – "Worst case" analysis

	QALYs	Incremental QALYs	Cost	Incremental cost	Incremental cost per QALY gained (ICER)
Strategy 0: No treatment	18 062.95	-	€21 709 119.21	-	-
Strategy 1: Treatment from stage F3	20 335.45	2 272.50	€72 332 958.37	€50 623 839.16	€22 276.71
Strategy 2: Treatment from stage "F2" (blood tests + elastography)	20 783.68		€83 941 978.39		Extended dominance*
Strategy 3: Treatment if the blood tests for fibrosis are positive	20 845.14	509.69	€84 841 101.03	€12 508 142.67	€24 540.62
Strategy 4: Treating all patients	20 899.80	54.66	€87 453 065.57	€2 611 964.54	€47 786.16

*Extended dominance is a situation where a combination of two interventions is less expensive and as or even more effective than another intervention. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life years.

4. BUDGET IMPACT

Given the high cost of the treatments and the relatively significant numbers of patients involved, especially in strategies 3 and 4, the choice for one strategy or another will inevitably also hinge on its estimated budget impact. To prevent putting an undue strain on the health insurance budget, we propose **putting a progressive reimbursement system in place**, starting with a restrictive scheme (the sickest patients) and moving towards a more inclusive scheme (all patients - see the diagram below). Adjustments at two-year intervals (or more where warranted by budget restraints) would progressively see the pool of patients requiring treatment drained, before reimbursement is extended to more patients.

First stage: Strategy 2:

Treating all patients from stage F2, i.e. positive to the elastography (Fibroscan ≥ 7.2 kPa or ShearWave ≥ 7.1 kPa or ARFI ≥ 1.32 m/s)

AND

to the blood tests (+ FIB4 > 1.45 or Fibrotest ≥ 0.49)

Second stage: Strategy 3:

Treating all patients whose blood tests are positive (+ FIB4 > 1.45 or Fibrotest ≥ 0.49)

Third stage: Strategy 4

Treating all HCV-positive patients

However, we have no way of predicting how many patients will be tested each year and how many will be eligible for treatment, because, aside from the fact that little is known about the epidemiology of the disease in Belgium, they are also uncertainties in relation to the performance of the tests and the profile of patients currently infected (fibrosis score, naive patient or not, IDU or not, etc.). Neither do we know to what extent a broadening of the reimbursement criteria will encourage clinicians to test for hepatitis C and start new therapies. Thus, we had to base our estimate of the number of new patients tested each year on purely hypothetical figures (see table 5). **To prevent a budgetary drift, we insist that a monitoring system must be put in place.**

Table 5 – Phasing of strategies 2-3-4

Year	Treatment strategy	Assumed number of patients tested	Range
Year 1	Strategy 2: Treatment from “F2” (blood tests + elastography)	3000	2000-3500
Year 2	Strategy 2: Treatment from “F2” (blood tests + elastography)	3000	2000-3500
Year 3	Strategy 3: Treatment if the blood tests for fibrosis are positive	3000	2000-3500
Year 4	Strategy 3: Treatment if the blood tests for fibrosis are positive	3000	2000-3500
Year 5	Strategy 4: Treating all patients	3000	2000-3500
Year 6	Strategy 4: Treating all patients	2500	2000-3000
Year 7	Strategy 4: Treating all patients	2000	1500-2500
From year 8	Strategy 4: Treating all patients	1500	1000-2000

Figure 2 shows the overall budget impact of the three stages described above until 2025 (2030 in the scientific report), based on the model's baseline parameters (see table 6 for the handle of the uncertainty surrounding these parameters).

The results presented in table 6 take the cost of medical care that is prevented (notably liver cancer, transplants) as a result of this three-phase strategy into account, by comparing the budgetary impact of this strategy to a no-treatment strategy (incremental analysis).

To highlight the considerable uncertainty around this surrounding budgetary impact analysis, various scenarios are presented in table 6 (scenarios on prices, on the number of patients who will be tested, and on the best-case/worst-case scenarios, retaining, within the range of potential values for each uncertain parameter, the value that most/least favours treating the population at an early stage of the illness).

Figure 2 – Budget impact of a gradual expansion as described in table 5 (2017-2025)

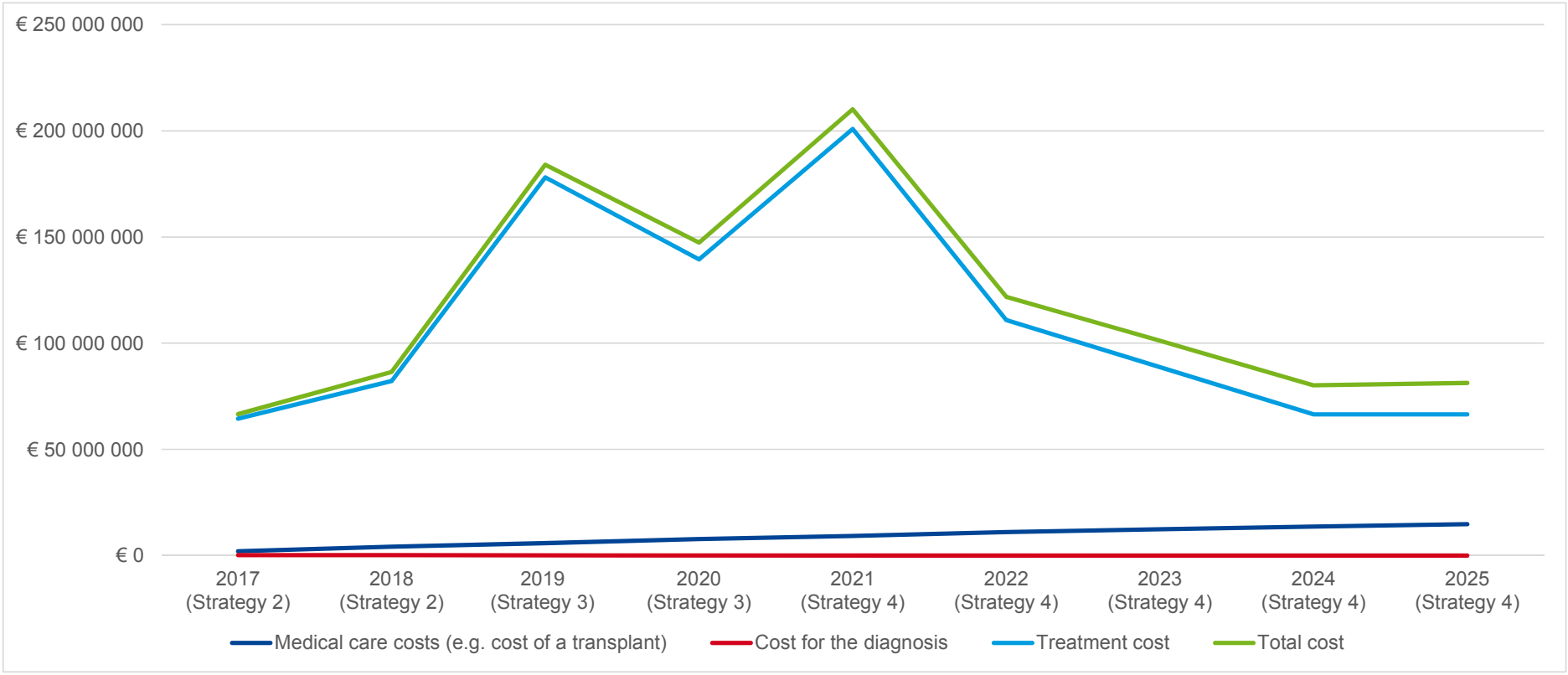


Table 6 – Budget impact of a gradual expansion (see table 5) compared to "no treatment" (2017-2023), treatment of the uncertainty included

Scenarios:	Incremental costs	Strategy 2 (F2) 2017	Strategy 2 (F2) 2018	Strategy 3 (blood tests +) 2019	Strategy 3 (blood tests +) 2020	Strategy 4 (everyone) 2021	Strategy 4 (everyone) 2022	Strategy 4 (everyone) 2023
(1) Cost of the treatments								
€17 500 (€21 000, ≥ F4)	Medical care costs	-€ 420 079	-€ 1 030 811	-€2 962 430	-€5 098 991	-€7 960 514	-€10 552 265	-€13 259 738
	Total	**€26 198 044**	**€33 056 955**	**€72 817 800**	**€53 905 619**	**€77 609 907**	**€36 228 844**	**€24 165 149**
€35 000 (€42 000, ≥ F4)	Medical care costs	-€ 420 079	-€ 1 030 811	-€2 962 430	-€5 098 991	-€7 960 514	-€10 552 265	-€13 259 738
	Total	**€52 617 700**	**€66 946 253**	**€148 503 860**	**€112 816 059**	**€163 180 327**	**€83 009 952**	**€61 590 036**
€40 000 (€63 000, ≥ F4)	Medical care costs	-€ 420 079	-€ 1 030 811	-€2 962 430	-€5 098 991	-€7 960 514	-€10 552 265	-€13 259 738
	Total	**€64 195 636**	**€81 340 543**	**€175 255 114**	**€134 486 114**	**€192 938 913**	**€100 326 438**	**€75 443 225**
€70 000 (€84 000, ≥ F4)	Medical care costs	-€ 420 079	-€ 1 030 811	-€2 962 430	-€5 098 991	-€7 960 514	-€10 552 265	-€13 259 738
	Total	**€105 457 010**	**€134 724 849**	**€299 875 980**	**€230 636 939**	**€334 321 167**	**€176 572 170**	**€136 439 810**
(2) Number of patients tested								
Year 1-6: 2000; year 7: 1500; ≥ year 8: 1000	Medical care costs	-€280 052	-€687 207	-€ 1 974 953	-€3 399 327	-€5 307 009	-€7 131 094	-€8 994 097
	Total	**€42 797 091**	**€ 54 227 029**	**€116 836 743**	**€89 657 409**	**€128 625 942**	**€81 571 868**	**€57 533 125**
Year 1-5: 3000; year 6: 2500; year 7: 2000; ≥ year 8: 1500	Medical care costs	-€ 420 079	-€ 1 030 811	-€2 962 430	-€5 098 991	-€7 960 514	-€10 552 265	-€13 259 738
	Total	**€64 195 636**	**€81 340 543**	**€175 255 114**	**€134 486 114**	**€192 938 913**	**€100 326 438**	**€75 443 225**
Year 1-5: 3500; year 6: 3000; year 7: 2500; ≥ year 8: 2000	Medical care costs	-€490 092	-€ 1 202 613	-€3 456 169	-€5 948 823	-€9 287 266	-€12 335 039	-€15 544 356
	Total	**€74 894 909**	**€94 897 300**	**€204 464 300**	**€156 900 466**	**€225 095 398**	**€120 719 405**	**€95 334 347**
(3) Worst and best-case scenarios								
Best-case scenario	Medical care costs	-€446 877	-€ 1 137 150	-€3 622 580	-€6 080 485	-€9 456 562	-€12 187 762	-€14 875 248
	Total	**€20 043 791**	**€21 494 229**	**€37 816 115**	**€31 121 113**	**€61 884 125**	**€26 342 719**	**€14 022 612**
Worst-case scenario	Medical care costs	-€83 394	-€52 248	-€282 672	-€701 438	-€ 1 294 846	-€2 069 792	-€2 987 783
	Total	**€137 584 285**	**€197 782 440**	**€424 327 723**	**€311 374 541**	**€401 865 063**	**€250 948 037**	**€207 860 408**

The analysis demonstrates the extent of the risk of a budgetary explosion, even in the baseline scenario (see figure 2). As the impact will strongly depend on the number of eligible patients, which, as stated above, is completely uncertain, that number will have to be monitored on a regular basis (quarterly) and, where necessary, the strategy will have to be adjusted in function of the results obtained in practice, e.g. by slowing down the broadening of the criteria.

Needless to say, the budgetary impact will be dictated by the cost of the therapy. If one wants to stick to an overall budget of, for instance, maximum € 40 000 000 a year, the total cost for a non-cirrhotic patient should drop to the levels described in the frame below (according to the baseline analysis).

Maximum total treatment cost (for a non-cirrhotic patient) required to maintain the various budget limits associated with the cost of these therapies, based on the baseline analysis.

Budgetary limit	Maximum treatment cost for years 1 and 2 "treatment from F2"	Maximum treatment cost for years 3 and 4 "treating all patients whose blood tests for fibrosis are positive"	Maximum treatment cost from year 5 "treating all patients"
€20 000 000	€9 736	€4 491	€3 982
€40 000 000	€19 471	€8 983	€7 964
€60 000 000	€29 207	€13 474	€11 946
€80 000 000	€38 942	€17 965	€15 928
€100 000 000	€48 678	€22 456	€19 910

5. TOWARDS AN ERADICATION?

Some articles sponsored by the industry highlight the perspective of eradicating or eliminating HCV on the basis of models that describe linear increases in the number of patients treated. In reality, given that the virus seems to be increasingly prevalent among high-risk groups, which are harder to reach than the average population, these forecasts seem fairly unrealistic at this stage. In fact, the specific characteristics of these populations typically call for significant outreaching efforts and the implementation of proactive approaches, integrated services and other targeted courses of action, yet, without much hope of a 100 % success rate.

5.1. Intravenous drug users

It has been proffered that the treatment of hepatitis C among IDUs could effectively and cost-efficiently reduce the transmission of the virus but this theory of “prevention through treatment” has never been proven by epidemiological studies or comparative trials.

The data rather show that, in this population, treatment is not widespread. Literature gives a number of reasons for that fact: the lack of compliance and the rate of reinfection following treatment (arguments raised by professionals in the field), and the lack of access to diagnostic tests (argument raised by IDUs themselves). All of the above are compounded of course by a general lack of knowledge about the disease and the various treatments, and, lastly, by the lack of symptoms of the disease itself. The side effects of the therapies have also been raised as a factor but that argument should start carrying less weight with the availability of DAAs.

Some of the lessons learned from the HIV epidemic could be used again to combat the progression of hepatitis C in the IDU population, and notably the importance of putting a series of global, coordinated and multidisciplinary approaches in place. In Europe, interest groups have highlighted the need to develop a HCV management plan, which notably includes strategies such as improving access to screening, treatment and healthcare services, and the need to intensify Community-based efforts and harm reduction interventions to reduce the risks. Certain actions were already proposed by the Inter-Ministerial Health Conference on HCV and included in the “HCV Plan” (Belgian Official Journal [Moniteur Belge] 08.08.2014).

5.2. MSM (men who have sex with men)

In the MSM community, key issues are the international transmission via a highly connected network, and the uncertainties about the possibility of transmission to or via other population groups. Furthermore, it is currently difficult to foresee whether the increased availability of antiretroviral therapies to treat HIV and pre-exposure prophylaxis will also have an impact on the HCV epidemic and the preventive actions in this population.

5.3. Immigration

Immigration from countries where the prevalence of HCV is high could lead to an increase in HCV in our country, yet that issue is not widely documented. Egypt is considered to be the country with the highest prevalence of HCV in the world (>10%) while most of the other African countries have a prevalence of 2 to 3%. Infection rates are also relatively high in several Eastern European countries, Latin America, the former Soviet Union, the Middle East and Southern Asia. The inter-ministerial HCV plan foresees targeted screening of immigrants from high prevalence countries, but it is not clear how this can be operationalized (or whose competence this actually is).

According to the **recommendations of the *European Association for the Study of the Liver* (*EASL*):**

- Treatment of HCV should be ensured by a multidisciplinary team, experienced in the evaluation and the treatment of this infection;
- HCV-infected patients should receive advice on the importance of therapeutic compliance;
- Support services should form part of the clinical management of patients disadvantaged at a socio-economic level and migrants;
- For people who actively inject drugs, risk-reducing measures should be introduced. HCV treatment could be considered for IDU patients if they are favourably disposed to it and if they are prepared to regularly present themselves for the scheduled appointments. Potential interactions between the prescribed medicines and narcotics should also be taken into account;
- Patients should be advised against the consumption of alcohol while on antiviral therapy. Patients who consume alcohol on a regular basis should be given additional support while on antiviral therapy;
- Peer support should be considered as a means to improve the clinical management of HCV.

6. CONCLUSION AND DISCUSSION: TOWARDS A DIFFERENT REIMBURSEMENT MODEL?

In conclusion, the above analysis shows that, to keep the budget impact of the reimbursement of DAA treatments under control, the reimbursement criteria will have to be broadened on a progressive basis and a reduction in the price of the therapies should be obtained for each enlargement of the population. Furthermore, as the extent of the budget impact of this gradual expansion is difficult to predict in view of the various uncertainties that prevail, a quarterly monitoring of the number of patients treated and, in case of risk of budget drift, an urgent renegotiation of the prices and reimbursement criteria is required. We must also emphasise the need to collect more data on people infected with hepatitis C in Belgium so that our analyses can be validated. More specifically, data should be collected that would allow us to:

- Better determine the profile of people suffering from hepatitis C in Belgium: the age and patient gender; the genotype; the tests used, the stage of fibrosis.
- Assess the effectiveness of the treatment on the basis of Belgian data, in function of patient characteristics (for instance, on the basis of the stage of their fibrosis): the combination of pharmaceuticals administered (compounds and doses) and the duration of the therapy; the type of patient (naive or experienced; and if experienced, what treatments were given in the past); the SVR rate; the impact on the quality of life, measured by means of a generic instrument like the EQ-5d at various time intervals; and, ideally, a follow-up of relapses and reinfections (more long-term follow-up).

From a clinical and public health point of view, the progressive expansion we propose is not the best strategy however. The ideal would be to treat *all* patients carrying the virus as early as possible, before their condition deteriorates (strategy 4). But this inclusive strategy would require an even more substantial reduction in the cost of these treatments if the health insurance budget is to stay afloat.

We know that the authorities currently lack the relevant bargaining power to address these issues. What's more, Belgium is not the only country to find itself in this situation; the inflated prices of certain innovative medicines are putting the authorities of many countries in a difficult position. On the other hand, this could also be an opportunity to test innovative approaches.

Various options could be investigated:

- Collaborations with other countries: the larger the coalition represents patients, the more weight it will carry in the discussions. Belgium recently signed a declaration of intent with the Netherlands, the Grand Duchy of Luxembourg and Austria with a view to jointly negotiating the reimbursement of certain pharmaceuticals. Initially, this agreement was concluded mainly with orphan drugs in mind but there is nothing to prevent a pilot study on hepatitis C therapies from being set up within this framework.
- Organising a call for tenders with a view to granting a preferential reimbursement (by genotype and for an initial therapy) to the company that offers the most favourable terms. This could not only be done on a Belgian but also on a European scale. In fact, the mechanism of joint procurement agreements to purchase medical countermeasures the European Commission developed could be envisaged if the European countries decide to put a joint preventive treatment strategy in place (http://ec.europa.eu/health/preparedness_response/joint_procurement/index_fr.htm).
- Scrutinising the research market to identify new promising products in development stage II or III and purchasing the patents of developers so that they can subsequently be put on the market at a relatively low cost.

KCE, and its Dutch counterpart ZIN, have recently embarked on a process of reflection on the various alternative scenarios in the mid to long term. For further details, see KCE report 271 (https://kce.fgov.be/publication/report/future-scenarios-about-drug-development-and-drug-pricing)

RECOMMENDATIONS[a]

To the Ministry of Social Affairs and Public Health and to the RIZIV-INAMI:

- **In order to keep the budget impact of the new-generation direct acting antivirals (DAAs) therapies under control: progressively broaden the reimbursement criteria for these therapies.**
- **Given that it is impossible to foresee with certainty how many people will be tested and will be eligible for treatment: organise a quarterly monitoring of the number of patients treated. The possibility to "urgently" review the reimbursement conditions (negotiated prices and/or eligible population) in case of risk of budget overrun should also be provided for.**
- **Given the public health priority which entails access to these new expensive therapies for all infected patients: explore alternative avenues to purchase these medicines, such as a joint procurement agreements with other countries.**
- **To enhance the quality of future (economic) evaluations of these treatments on the basis of documented Belgian data and to validate our model: link the conventions to the collection of data so as to gain a clearer understanding of the profile of patients suffering from hepatitis C in Belgium and to assess the effectiveness of the therapy on the basis of Belgian data, as the RIZIV-INAMI "Hepatitis C" Working Group already recommends. However, as long as the prices negotiated in conventions remain confidential, only the people involved in the conclusion of these conventions will be in a position to assess the true economic impact.**

[a] The KCE only is responsible for its recommendations.

COLOPHON

Title:	Towards an expansion of the reimbursement conditions for Hepatitis C therapies? – Summary
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