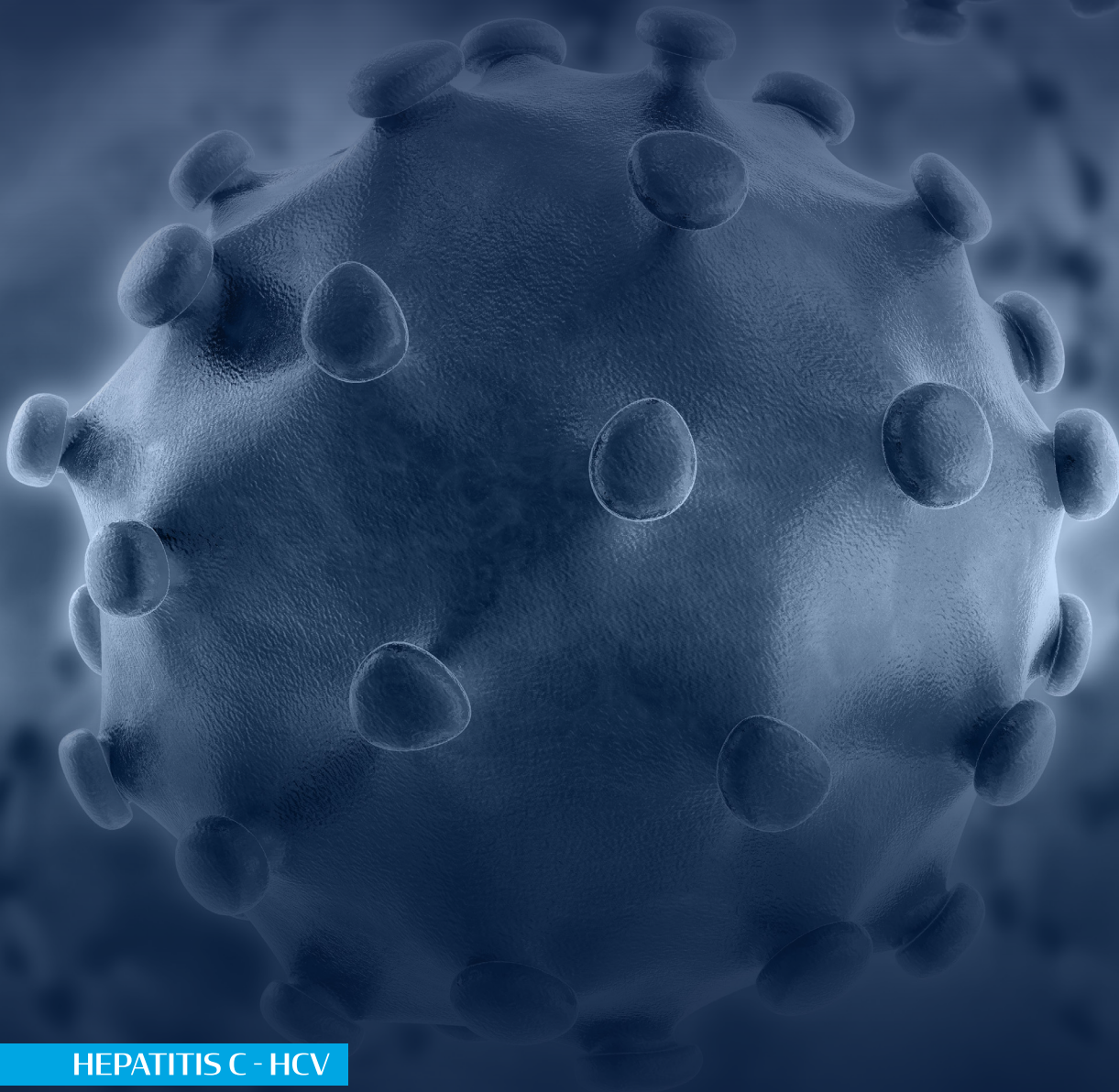


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MONOGRAPHY

PHARMACOLOGICAL AND PHARMACOECONOMIC
ASSESSMENTS ON THERAPEUTIC EQUIVALENCE
OF ANTI-HCV DRUGS



HEPATITIS C - HCV



PHARMACOLOGICAL AND PHARMACOECONOMIC ASSESSMENTS ON THERAPEUTIC EQUIVALENCE OF ANTI-HCV DRUGS

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ABSTRACT

The new challenge for this decade is to understand which strategy should be implemented to continue the HCV elimination plan in Italy, considering separate factors: on the one hand the further expansion of patient recruitment criteria by AIFA (to date 12) and on the other the conclusion of the three-year period of innovative status with the consequent exit from the innovative

drugs fund. Moreover, pursuant to Law 135/2012 (ex-Article 15, paragraph 11-ter), the Veneto Region has requested the evaluation of therapeutic equivalence for the medicines Epclusa® and Maviret® to allow centralised purchases of the two fixed-dose combinations through competing calls for tenders. The CTS has issued a positive opinion to Veneto Region request. The goal of this paper

is to discuss the criteria AIFA applied to grant the therapeutic equivalence to the two pangenotypic and panfibrotic treatments approved for hepatitis C and if the drugs can be evaluated as equivalent providing clinical and pharmacological evidence, also discussing pharmacoeconomic aspects.

Italy has played a key role in implementing the elimination plan for HCV infection by 2030, promoted by the World Health Organisation in its paper "Global health sector strategy on viral hepatitis 2016–2021 Towards ending viral hepatitis" (June 2016)¹, and is to date one of the nine countries worldwide in line with the WHO objectives achievement².

It is well recognised that the treatment landscape for anti-HCV therapy has radically changed over the last decade, moving from prolonged treatments with the peg-interferon (peg-IFN) plus ribavirin (RBV) association, characterised by poor efficacy and burdened by a sub-optimal safety profile and contraindications, to the oral second-generation Direct-acting antivirals (DAAs), now able to provide a sustained virologic response in over 90% of all cases.

In a few cases, such as the one of DAAs for treating hepatitis C, innovation in the drugs field has substantially contributed to changing the therapeutic and care scenario. After approval of telaprevir and boceprevir, the first signs of a revolution were expected. This therapeutic success has been guaranteed, at least in Italy, at a cost that is far lower than initial expectations. In fact, at the time of the marketing authorisation in the USA, the third revolutionary DAA had been announced at a list price of approximately 80,000 \$ by Gilead Sciences Inc., while in Italy sofosbuvir was reimbursed by AIFA (Italian Medicines Agency) on 5 December 2014.

The average price paid for the treatment of the first 50,000 patients was about

14,000 €, a price that came from one of the first price-volume agreements ever adopted by AIFA as part of a 500 million € fund dedicated to innovative drugs.

Since the approval of the first DAA (AIFA update on 11 May 2020), 208,593 patients have started HCV therapy in Italy³ in over 200 prescribing centres, with elimination rates near to 100%, and consequent implications for patients health and NHS sustainability, such as decline in the number of liver transplants performed both in patients with decompensated cirrhosis due to HCV (minus 60%) and in those with hepatocellular carcinoma associated with HCV (minus 41%) and improvement of the survival of liver transplant recipients with HCV-related liver disease⁴; decrease in the rate of hepatocellular carcinoma development and recurrence^{5,6}.

In the meanwhile, the cost of treatments has progressively fallen thanks to the introduction on the market of new DAAs and combinations that have contributed to the reduction of prices, to the point of reaching sustainable cost-therapy for a treatment able to change the natural history of the disease.

This is a success for public healthcare and for the NHS thanks to a long-term strategy born out of the close collaboration between AIFA, Regional administrations, the national hepatological scientific community, patient associations and the industry.

The challenge for the next decade is to understand which strategy should be

implemented to continue the HCV elimination plan in Italy, considering separate factors:

1. the further expansion of patient eligibility and recruitment through AIFA criteria (to date 12 criteria)⁷
2. the expiration of the three-year period of innovative status of some of these therapies, with the consequent exit from the innovative drugs fund
3. the CTS positive opinion, adopted by AIFA Director General on 16 December 2019, regarding the evaluation of therapeutic equivalence, requested by the Veneto Region, for the medicines Epclusa® and Maviret®⁸ which may open to a widespread use of this tool for cost-containment policies.

Regarding the latter point, "the evaluation of therapeutic equivalence is a method through which it is possible to compare medicines containing different active ingredients in order to identify, for the same indications, areas of therapeutic superimposability in which, in the light of scientific knowledge, clinical differences are not relevant in terms of efficacy and safety".

With its Decision no. 818/2018, AIFA has regulated the procedure and has defined the criteria to establish therapeutic equivalence for the purpose of purchasing drugs in competing calls for tenders⁹:

1. Be active ingredients for which there is experience of use, intended as a period of reimbursement by the National Health Service of at least 12 months.

2. Have evidence of efficacy coming
 - from trials that do not allow the demonstration of one drug's superiority over the other (for example trials vs. placebo), or
 - from head-to-head trials that do not provide for a hypothesis of superiority (e.g. comparisons through equivalence or non-inferiority trials).
3. Belong to the same 4th level ATC class.
4. Have superimposable main therapeutic indications (also for target sub-populations), as per section 4.1 of the SmPC.
5. Use the same administration route.
6. Provide for a posology that allows a substantially superimposable intensity and duration of treatment.

On 19 April 2019, the Veneto Region has requested the evaluation of therapeutic equivalence for the medicines Epclusa® and Maviret® to allow centralised purchases of the two fixed-dose combinations through competing calls for tenders, setting the requirement share that will be the subject of the equivalence tender at 60% (patients meeting AIFA eligibility criteria 1, 3, 4, 5, 7, 8, 9, 11).⁸

In the application, the Veneto Region concludes that “both medicines have a pangenotypic action, with a duration of treatment, in the population subject of the equivalence request, that varies between 8 (in subjects without cirrhosis

treated with Maviret®), 12 weeks (in subjects treated with Epclusa® and in subjects with compensated cirrhosis treated with Maviret®) and 16 weeks (in GT3 subjects previously exposed to PegIFN/RBV+SOF or SOF/RBV and retreated with Maviret®). In the absence of comparative studies proving relative efficacy of the two drugs, we do not believe that the difference in terms of treatment duration can determine a clinically significant advantage of one treatment rather than the other. Overall, therefore, limited to the populations for which equivalence is requested, the treatment patterns appear to be substantially superimposable. In the absence of comparative studies and indirect comparative analyses via network meta-analysis that show the relative efficacy of the two medicines, it is not believed that the difference in terms of treatment duration can determine a clinically significant advantage. On comparing the pooled analysis data from the pivotal trials of the two medicines, no substantial differences emerge in terms of efficacy and tolerability between the two treatments. Populations for whom one of the two drugs is not recommended (subjects with decompensated cirrhosis, CKD under dialysis treatment, previous treated with NS5A and/or NS3/4 inhibitors), populations with GT3 in whom treatment with Epclusa® or Maviret® would require the addition of RBV or longer

treatment times and patients with recurring, post-transplant hepatitis in which the supporting evidence are less robust are excluded from the evaluation of equivalence and specific pharmacological interactions must also be taken into consideration”.

According to the procedure, the CTS expressed a preliminary opinion in July 2019, to which the marketing authorization holders Gilead Sciences and Abbvie had the possibility to make observations on 1st October 2019. In the CTS meeting of 6-8 November 2019, the CTS adopted a final positive opinion on the request by Veneto Region, which has been published on 16 December 2019.⁹

We have assessed the therapeutic equivalence between Maviret® and Epclusa® from the pharmacological perspective considering every single aspect (therapeutic indications, mechanism of action, pharmacodynamics and pharmacokinetics parameters, clinical efficacy and safety), that should be taken into account and then discussed its implication regarding therapeutic equivalence, in the light of the recommended use stated by national and international guidelines¹⁰⁻¹², also from an economic point of view.



PHARMACOLOGICAL DISSERTATION^{13,14}

THERAPEUTIC INDICATIONS

Epclusa®: treatment of chronic hepatitis C virus (HCV) infection in adults.

Maviret®: treatment of chronic hepatitis C virus (HCV) infection in adults and in adolescents aged 12 to <18 years.

PHARMACEUTICAL FORMS AND ROUTE OF ADMINISTRATION

The pharmaceutical form (film-coated tablets) and the route of administration (oral) are identical.

POSODOLOGY

Epclusa®

- The recommended dose of Epclusa is one tablet, taken orally, once daily with or without food.
- Recommended treatment and duration for all HCV genotypes:

Patient population	Treatment and duration
Patients without cirrhosis and patients with compensated cirrhosis	Epclusa for 12 weeks Addition of RBV may be considered for genotype 3 HCV infected patients with compensated cirrhosis*
Patients with decompensated cirrhosis ^a	Epclusa + ribavirin for 12 weeks

* This population is excluded from the one for which the equivalence request was made

^a Includes patients co-infected with human immunodeficiency virus (HIV) and patients with recurrent HCV post-liver transplant

Maviret®

- Recommended dose: three tablets taken orally, once daily at the same time with food.
- Recommended treatment and duration for all HCV genotypes:

Patient population	Treatment and duration	
	Naïve	Experienced (failure of prior therapy with peg-IFN + ribavirin +/- sofosbuvir, or sofosbuvir + ribavirin)
Patients without cirrhosis	8 weeks	8 weeks (16 weeks GT3)
Patients with compensated cirrhosis	8 weeks	12 weeks (16 weeks GT3*)

* Population is excluded from the one for which the equivalence request was made

Both medicinal products are pangenotypic drugs. The intensity of the therapeutic regimen may be defined as comparable, since in both cases it is a once daily administration of oral tablets: 1 tablet for Epclusa®, 3 tablets for Maviret®.

PHARMACODYNAMIC PROPERTIES

Epclusa® - Pharmacotherapeutic group: Direct acting antiviral - ATC code: J05AP55

Maviret® - Pharmacotherapeutic group: Direct acting antiviral - ATC code: J05AP57

Mechanism of action

Epclusa®

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Velpatasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions.

Maviret®

Glecaprevir is a pan-genotypic inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein and is essential for viral replication. Pibrentasvir is a pan-genotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly.

Finally, pibrentasvir and velpatasvir share the same mechanism of action, while glecaprevir and sofosbuvir has a different mechanism of action. When the active ingredients are combined in the pharmaceutical preparations, it is clear that they do not share the same mechanism of action. In addition, the potency of the various active ingredients is different.

PHARMACOKINETIC PROPERTIES

Pharmacokinetic elements of the DAA considered in the analysis

	glecaprevir	pibrentasvir	velpatasvir	sofosbuvir
Mechanism of action	NS3/4 ^o protease inhibitor	NS5A pan-genotypic inhibitor	NS5A pan-genotypic inhibitor	NS5B pan-genotypic polymerase inhibitor
Protein bond	97,5%	> 99,9%	> 99,9%	61-65%
Half-life	6 h	23-29 h	15 h	0,5 h (sofosbuvir), 25 h (inactive metabolite GS-331007)
Metabolism	CYP3A Substrate: P-gp, BCRP, OATP1B1/3 Weak inhibitor: CYP3A e UGT1A1 Inhibitor: P-gp, BCRP, OATP1B1	CYP3A4 Substrate: P-gp, BCRP (probably) Inhibitor: P-gp, BCRP, OATP1B1 Weak inhibitor: CYP3A e UGT1A1	CYP2B6, 2C8, 3A4 Substrate: CYP3A4, 2C8, 2B6; OATP1B1, OATP1B3, P-gp, BCRP Inhibitor: P-gp (weak), OATP1B1, 1B3, 2B1(weak), BCRP (moderate)	Quickly activated to active triphosphate (GS-461203) Substrate: P-gp, BCRP
Elimination	In feces 92,1%, in urine 0,7%	In feces 96,6%, in urine 0%	In feces > 94%, in urine 0,4%	80% in urine, 14% in feces (mainly as GS-331007)

CLINICAL EFFICACY AND SAFETY

As there are no direct comparative studies between the two medicinal products, it would be suitable to consider the pivotal studies that have involved patients with similar characteristics to the population that is the subject of the therapeutic equivalence evaluation.

Epclusa®

The efficacy of Epclusa® was evaluated in three Phase 3 studies in patients with genotype 1 to 6 HCV infection with or without compensated cirrhosis, one Phase 3 study in patients with genotype 1 to 6 HCV infection with decompensated cirrhosis, one Phase 3 study in HCV/HIV-1 co-infected patients with genotype 1 to 6 HCV infection and one Phase 2 trial in patients with HCV infection and ESRD requiring dialysis. The data and the pooled analysis reported in the product's EPAR show an high sustained virological response rate and a good safety profile: overall percentages of SVR12 was 98% (99% in subjects without cirrhosis and 96% in subjects with compensated cirrhosis). In an observational trial conducted in 19/31 prescribing centres in the Puglia Region between June 2017 and May 2018, 1429 subjects treated with SOF/VEL 400/100 mg for 12 weeks were evaluated (RBV had been added in just 41 subjects)¹⁵. In this non-selected cohort of subjects the global proportion of SVR12 was 98.7% (95%CI 97.8%-99.1%); 98.3% (95% CI: 96.7%-99.1%) in 587 F3-F4 subjects and 98.6% (95% CI: 97.4%-99.3%) in those F0-F2 (p = 0.65). In another perspective trial conducted in 5 Italian centres the objective was to evaluate the efficacy of SOF/VEL, without RBV, in subject infected by GT3 HCV with and without decompensated cirrhosis and evidence of portal hypertension [16]. From June 2017 to August 2018, 227 cirrhotic subjects were evaluated, with 205 showing signs of portal hypertension (111 of them had an elastography result of >20 kPa). The SVR12 rate was found to be 97.6% (95% CI 94.4–98.9), ranging between 99.1% (95% CI 95.7–99.8) in subjects with >20KPa and 95.8% (95% CI 89.5–98.3) in those with <20 KPa (p = 0.18).

Maviret®

A pooled analysis was recently conducted on the 9 main phase II and phase III pivotal trials carried out on subjects with GT1-6 without cirrhosis and treated with GLE/PIB (300 mg/120 mg) for 8 or 12 weeks¹⁷. The recruited subjects were naive or experienced for peg-IFN, RBV, and/or SOF; while the subjects infected with GT3 had to be treatment-naive. 2,041 subjects were included in the analysis. In the ITT population, SVR12 was achieved in 943/965 (98%; 95% CI 96.6–98.5%) subjects treated for 8 weeks and in 1,060/1,076 (99%; 95% CI 97.6–99.1%) subjects treated for 12 weeks (with a non-statistically significant difference between the two regimens; p = 0.2). Integrated analyses of the pivotal clinical trials were carried out in relation to special populations, such as subjects with psychiatric diseases¹⁸ and elderly subjects¹⁹, highlighting excellent results in terms of efficacy and tolerability, in both cases. Such high rates of clinical efficacy were also confirmed in real practice studies [20-22]. When evaluating the data in Italian contexts, the NAVIGATORE-Lombardia Network analysis must be considered, when data of all the patients that started GLE/PIB between October 2017 and January 2018 were analysed²¹. In total, the data of 723 subjects were evaluated and SVR12 was achieved by 98% (8 vs. 12-week: 98%vs. 100%) patients with available data for the per protocol analysis. Another analysis of the Italian context refers to the multicentre, multiregional observational perspective MISTRAL (Maviret South iTaly ReAl Life) trial for which all the subjects who had started treatment with GLE/PIB in Campania, Puglia and Calabria were recruited²². In total, 1,177 subjects were recruited in 22 clinical centres and 1,163/1,177 (99%) subjects obtained a SVR. 118 (10%) drug addicts were also recruited in the trial, in whom high SVR rates were observed (95% in GT3 and 100% in other genotypes).

COMPARISON BASED ON THE THERAPEUTIC EQUIVALENCE CRITERIA INDICATED BY AIFA

The individual criteria of therapeutic equivalence indicated by AIFA and applied to the case of the two drugs Epclusa® and Maviret® have been analysed in this section.

CRITERION 1 - SATISFIED ✓

The two drugs Epclusa® and Maviret® were both approved by AIFA in 2017, respectively through Decision no. 780/2017 published in the Official Journal no. 96 of 26-04-2017 and by Decision no. 1612/2017 published in the Official Journal no. 226 of 27-09-2017.

CRITERION 2 - NOT SATISFIED ✗

- Although, Epclusa® and Maviret® both show high efficacy in pivotal studies, evidence of efficacy for the analysed anti-HCV drugs does not come from head-to-head trials or from indirect comparative analyses via networks meta-analysis, therefore the therapeutic equivalence between the two drugs cannot be confirmed or excluded. Moreover, from a methodologic perspective, it would be not scientifically correct to compare data collected in different times, and from trial with peculiar inclusion and exclusion criteria. As the enrolled population show different characteristics, before a comparison, methods to minimize and correct these biases should be applied.

- The evaluation by the Veneto Region is based on comparisons of efficacy and safety data taken from pivotal clinical trials. This type of comparison must take into consideration the different enrolled populations, statistical variability etc, to not be characterised by a high degree of arbitrariness.

- Although no head to head clinical trials are available, the performances of the viral NS5A inhibitors, pibrentasvir and velpatasvir, ingredients of the two therapeutic regimens Maviret® and Epclusa® were compared in vitro. The in vitro differences can be translated into clinical-therapeutic differences, as proven in the realm of randomised and controlled clinical trials.

CRITERION 3 - SATISFIED ✓

The two drugs belong to the same 4th level ATC class. However, it must be underlined that according to the WHO definition, the ATC system has purely classificatory purposes and in fact, the recent WHO guidelines on drug classification state that the “assignment to different ATC groups does not mean a difference in therapeutic effectiveness and assignment to the same ATC group does not indicate therapeutic equivalence”²³.

CRITERION 4 - NOT SATISFIED ✗

- The therapeutic indications of the analysed anti-HCV drugs are not superimposable in the various target sub-populations (also not numerically identifiable with certainty), therefore the drugs cannot be considered equivalent based on the indication:
- Maviret® is indicated in adolescents aged 12 to 18 and in adults, while Epclusa® is only indicated in adults.
- Maviret® is not recommended in patients with moderate liver impairment (Class B according to Child-Pugh) and is contraindicated in patients with severe liver impairment (Class C according to Child-Pugh), unlike Epclusa® for which no dose adjustment is needed according to the severity of liver impairment;
- Drug-drug interactions are a key factor in the treatment of patients with HIV-HCV coinfection. The EASL guidelines for treatment of patients affected by HIV-HCV clearly indicate a non-superimposability between the various treatments. For example, Maviret® is contraindicated with regimens containing atazanavir and is not recommended with other HIV protease inhibitors¹².

CRITERION 5 - SATISFIED ✓

The two drugs share the same oral pharmaceutical form. However, Maviret® must be taken with food¹⁴, while Epclusa® has no food interaction and can be taken with or without food¹³, differentiating characteristics to be taken into consideration for possible differences in absorption and therefore in drug

exposure. Moreover, only Maviret® has drug bio-availability data in the event the tablet is not swallowed whole (difficulty in swallowing due to rheumatological, oncological, otorhinolaryngologic and neurological pathologies and syndromes).

CRITERION 6 - NOT SATISFIED ✗

- There are differences in the posology patterns that further support the lack of superimposability between these drugs: Epclusa® and Maviret® do not always have the same treatment duration, as per recommendations and orientation documents. In fact, these change “substantially” in some specific settings, as clearly indicated in the AISF paper, leading to the non-observance of criterion 6²⁴.
- In addition to clinical reasons, the intrinsic value of a shorter duration of treatment can be traced to other factors too, such as, for example, an improved cost-benefit ratio, pursuit of quality of life, less exposure of the patient to the drug, lower risk of pharmacological interactions, shorter duration of co-administration of any other medicines, less commitment for the patient, organisational advantage for the healthcare facility where the patient is treated, possibility of easier treating of patients for whom the time factor is limiting or subjects who would potentially not adhere to the treatment.

Summing up our assessment, only criteria 1, 3 and 5 are satisfied (criteria 3 and 5 with some specifications). However, the aforementioned criteria have practically no impact on the conduct of the medical therapy in clinical practice.

Criterion 2 is not satisfied, as essential aspects for the prescription of a therapy, such as pharmacokinetics, pharmacodynamics, drug-drug interaction profile and potency are not taken into consideration.

The other two criteria (4 and 6, not satisfied according to our assessment) are those that can have a potential relevant impact on the clinical practice.

In particular, the fact that the indications and sub-populations of treatable patients are different does not meet AIFA criterion 4 of therapeutic equivalence.

Moreover, the different treatment durations ranging from 8 to 16 weeks, according to guidelines¹⁰⁻¹² and experts' opinion are substantially different, not

satisfying AIFA criterion of therapeutic equivalence.

CRITERIA	OBSERVATIONS
1. To be active ingredients for which there is experience of use (reimbursement by the National Health Service of at least 12 months)	SATISFIED ✓
2. To have proof of efficacy coming from trials that do not permit demonstration of superiority of one drug over the other, or head-to-head trials that do not provide for a hypothesis of superiority	Maviret® and Epclusa® do not have direct comparison trials, but the in vitro and in vivo data that subsequently suggested the indications recognised by scientific societies show differences in terms of pharmacokinetics, pharmacodynamics, drug-drug interactions profile, potency and duration of treatment that cannot be equalised, but are considered whether they are optimal in specific clinical cases.
3. To belong to the same 4 th level ATC class	SATISFIED ✓
4. To possess superimposable main therapeutic indications (also for target sub-populations)	• Maviret® is indicated in adults and adolescents aged 12 to 18. • Epclusa® is only indicated in adults and the addition of ribavirin can be taken into consideration for patients with GT3 HCV infection with compensated cirrhosis. Patients with liver impairment: • Maviret® is not recommended in patients with moderate liver impairment (Child-Pugh B) and is contraindicated in patients with severe liver impairment (Child-Pugh C). • Epclusa® does not require any dose adjustment in patients with mild, moderate or severe liver impairment (Child-Pugh A, B or C). Patients with kidney impairment: • Maviret® does not require any dose adjustment in patients with any kind of kidney impairment, including patients in dialysis. • Epclusa® was not evaluated in patients with severe kidney impairment (eGFR <30 ml/min/1,73 m²) or end-stage renal disease requiring haemodialysis.
5. To use the same administration route	SATISFIED ✓
6. To plan a posological pattern that allows treatment with a substantially superimposable intensity and duration	The posological pattern is substantially different for the two drugs. • Maviret® implies the assumption of three tablets taken orally once a day. • Epclusa® implies the assumption of a single tablet orally once a day. Duration of treatment varies greatly between drugs. • Maviret® needs a treatment duration of 8, 12 or 16 weeks depending on the treated patient population, HCV genotype, presence of cirrhosis and any previous treatments. • Epclusa® needs a treatment duration of 12 weeks independently of the treated patient population.

eGFR = estimated Glomerular Filtration Rate

The present analysis of the evidences available for the application of criteria used to assess the therapeutic equivalence by AIFA **has highlighted limits and weaknesses from a scientific point of**

view (in particular for criteria 2, 4 and 6). The conclusions stated above are the result of a specific analysis of the application of the criteria. Also considering the application for therapeutic equivalence

at 60% of treatments, as stated by the Veneto Region, this can only further intensify identified limits.

ECONOMIC DISSERTATION

The policy enacted by our national health service in recent years has undoubtedly contributed to pursuing the WHO goal, making Italy one of the most cutting-edge countries in the fight against HCV. According to the WHO, Italy is one of the countries that can achieve complete eradication of the virus thanks to the huge amount of work carried out in the last 5 years. The difficulty in identifying new target patients has already been proven by recent treatment dynamics, that have most certainly slowed down.

With 2020, a new phase of search for efficiency is starting, perhaps the most

difficult one. In fact, this implies an active search for all those that despite having contracted the disease, are not aware of it.

In 2018, the cost per capita for DAAs was € 6.85, 56.1% lower than in 2017²⁵ with almost the entire costs concentrated in the category of fix-dosed combination treatments. This reduction is clearly the result of a decrease in the number of patients as they are being progressively treated but is also due to the effect of a gradual drop in price.

In fact, thanks to the launch of new drugs and consequent negotiations, the therapy cost per patient has gone from

€ 14,000 in 2015 to approximately the current € 5,000²⁶, and will decrease by additional 9.75% after the loss of the innovation status.

This important result has been achieved thanks to the renegotiation of reimbursement conditions by AIFA, which has also fully eliminated the initial access restrictions linked to the severity of the disease and the restrictions on the number of patients to be treated.

CONCLUSIONS

The non-observance of all the 6 criteria from the therapeutic equivalence resolution in favour of partial equivalence for the acceptance of the Veneto Region's request in the case of HCV extends the concept of equivalence to any treatment, as there are almost always overlaps (or therapeutic alternatives) in treatments. This interpretation opens the scenarios for changes to rules on the market, with easily identifiable consequences.

The reference Italian scientific societies AISF and SIMIT, the patient association EpaC and Alliance against Hepatitis (ACE) have not positively received the

CTS opinion, believing it may complicate the virus elimination process and asking for the suspension of the opinion thus guaranteeing the possibility to clinicians to make treatment choice according to science and conscience and according to patients' characteristics [27]. The case of Epclusa® and Maviret® is extremely interesting since these drugs were the first ones to have obtained a positive opinion according to the therapeutic equivalence method, despite being part of a therapeutic class currently changing the natural history of a disease, already undergone to a continuous decrease in treatment cost due

to both the competitive landscape and AIFA ability in price negotiation.

A central approach like the one for price renegotiations, that has so far proven to produce economically and clinically important results, would seem to be preferable compared to a regional approach based on competition in regional calls for tender, which may actually increase differences, and feed contention in healthcare.

The hope is that a history that has so far been successful can continue towards the clear objective of eliminating hepatitis C in Italy.

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