Convegno

I NUOVI FARMACI PER HCV:
FREQUENZA DELLA PATOLOGIA, EVIDENZE DI EFFICACIA E SICUREZZA, STRATEGIE DI GESTIONE

10 luglio 2014

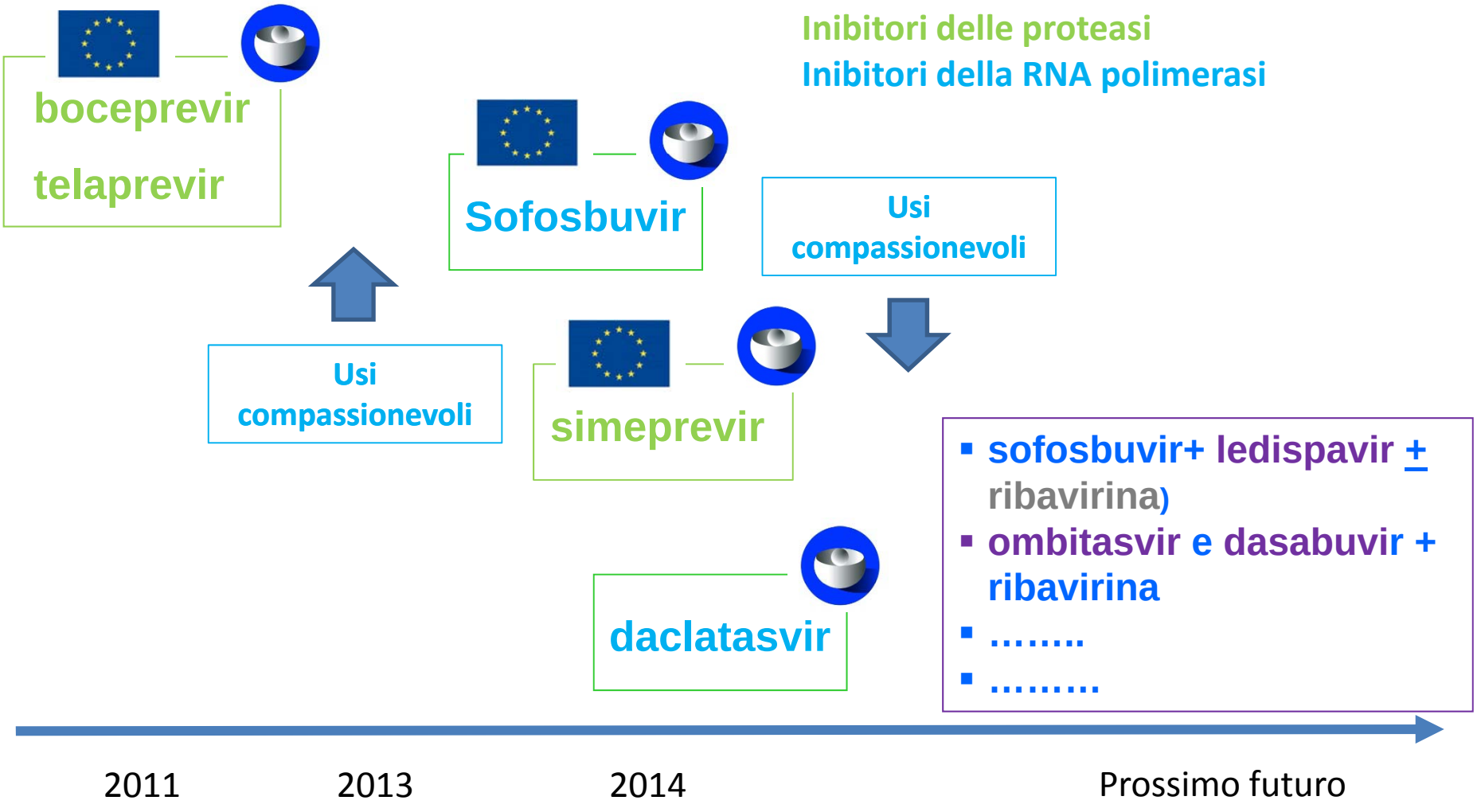
organizzato da
ISTITUTO SUPERIORE DI SANI
CNESPS - Farmacoepidemiolog

AGENZIA SANITARIA E SOCIALE REGIONALE
EMILIA ROMAGNA

12.20	**II Sessione** EVIDENZE DI EFFICACIA E ACCESSO AI FARMACI
	Moderatori: **M. Maggini, P. Popoli**
12.30	La prognosi nel paziente con epatite C **G. Taliani**
12.50	La revisione delle evidenze e indicazioni per la pratica clinica **M. Marzioni**
13.15	Discussione
13.30	Pranzo
14.30	L'accesso ai nuovi farmaci negli altri Paesi **G. Ippolito**
14.45	Discussione

Anna Maria Marata

I farmaci per l'epatite C: la situazione registrativa europea



Prezzo di sofosbuvir per 12 settimane di trattamento

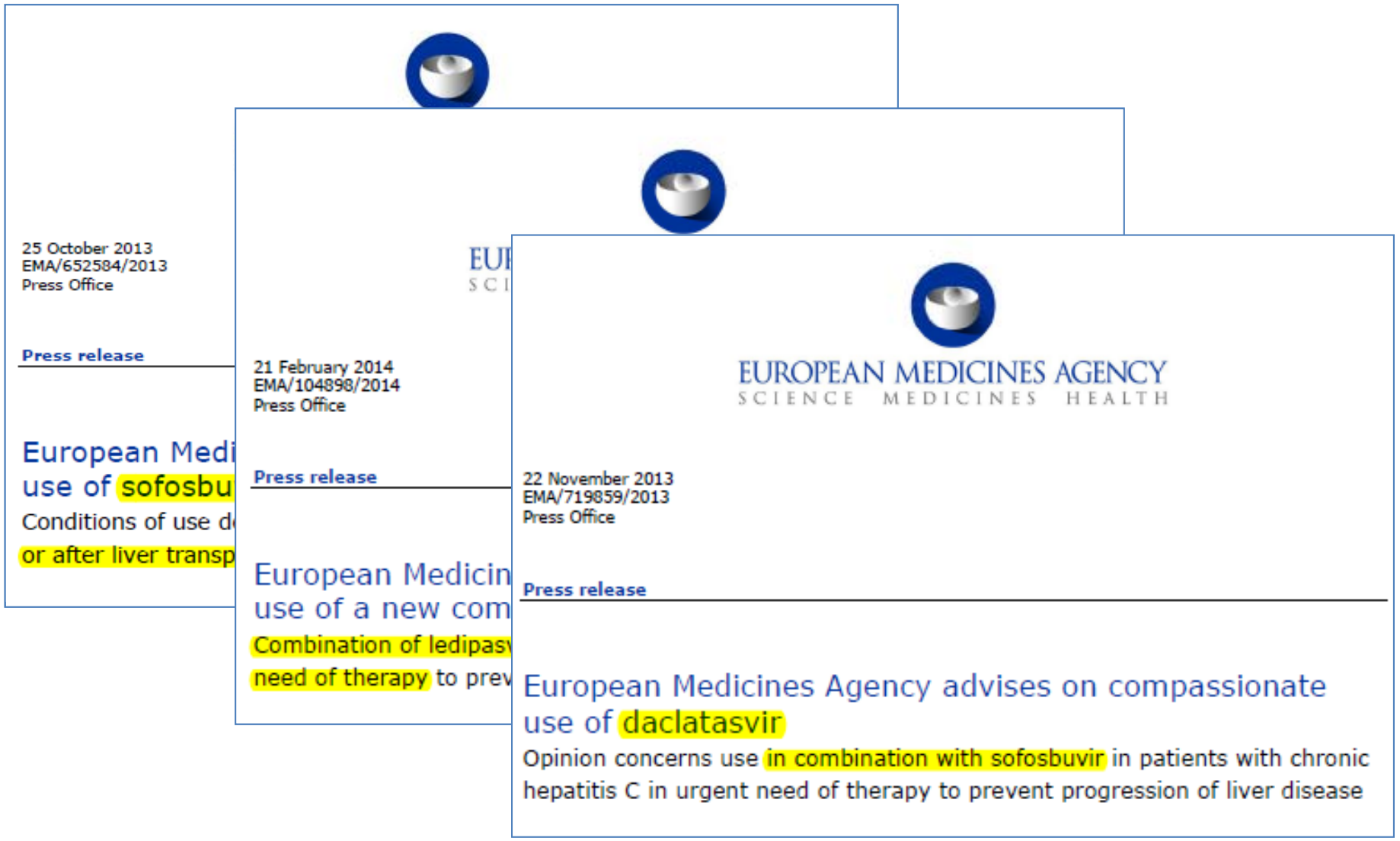
paese	€	USA $
USA	61.700	84.000
Regno Unito	41.900 35.000	57.000
Germania	48.500	66.000
Francia	56.000	76.000
Egitto	660	900
Mozambico, Kenya, Myammar,	660	900
India	660	900
Generico	95 - 198	130-270
Prezzo di produzione (stimato)	50 - 99	

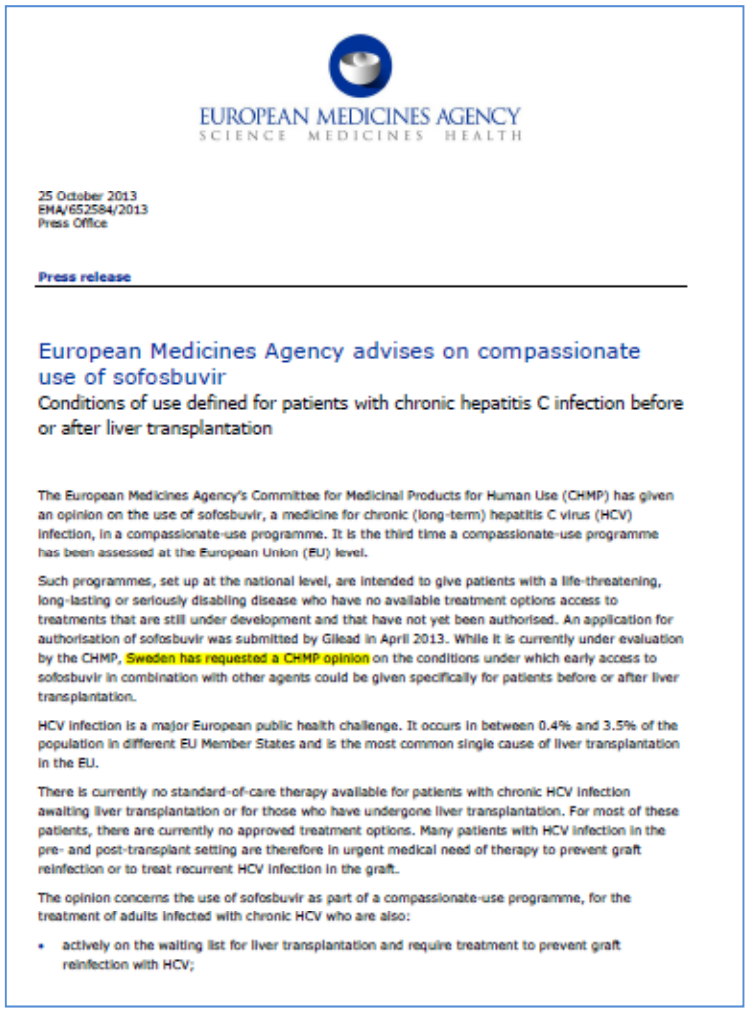
Sofosbuvir: Paesi europei in cui è commercializzato:

- Germania
- Regno Unito/Scozia
- Austria
- Svezia
- Finlandia
- Francia
- ……..

….Lista in continuo aggiornamento

Il primo accesso a questi farmaci è stato attraverso l'uso compassionevole: .....il parere di EMA





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 October 2013
EMA/652584/2013
Press Office

Press release

European Medicines Agency advises on compassionate use of sofosbuvir

Conditions of use defined for patients with chronic hepatitis C infection before or after liver transplantation

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has given an opinion on the use of sofosbuvir, a medicine for chronic (long-term) hepatitis C virus (HCV) infection, in a compassionate-use programme. It is the third time a compassionate-use programme has been assessed at the European Union (EU) level.

Such programmes, set up at the national level, are intended to give patients with a life-threatening, long-lasting or seriously disabling disease who have no available treatment options access to treatments that are still under development and that have not yet been authorised. An application for authorisation of sofosbuvir was submitted by Gilead in April 2013. While it is currently under evaluation by the CHMP, Sweden has requested a CHMP opinion on the conditions under which early access to sofosbuvir in combination with other agents could be given specifically for patients before or after liver transplantation.

HCV infection is a major European public health challenge. It occurs in between 0.4% and 3.5% of the population in different EU Member States and is the most common single cause of liver transplantation in the EU.

There is currently no standard-of-care therapy available for patients with chronic HCV infection awaiting liver transplantation or for those who have undergone liver transplantation. For most of these patients, there are currently no approved treatment options. Many patients with HCV infection in the pre- and post-transplant setting are therefore in urgent medical need of therapy to prevent graft reinfection or to treat recurrent HCV infection in the graft.

The opinion concerns the use of sofosbuvir as part of a compassionate-use programme, for the treatment of adults infected with chronic HCV who are also:

- actively on the waiting list for liver transplantation and require treatment to prevent graft reinfection with HCV;

L'obiettivo di EMA

The aim of the CHMP assessment and opinion on a compassionate-use programme of new medicinal products is to ensure a common approach, whenever possible, regarding the criteria and conditions of use under Member States' legislation. The opinion provides recommendations to the EU Member States that are considering setting up such a programme, and its implementation is not mandatory. In addition to describing which patients may benefit from the medicine, it explains how to use the medicine and gives information on safety. The assessment report and conditions of use of sofosbuvir in this setting will be published shortly on the Agency's website.

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L'obiettivo di EMA

The opinion concerns the use of sofosbuvir as part of a compassionate-use programme, for the treatment of adults infected with chronic HCV who are also:

- actively on the waiting list for liver transplantation and require treatment to prevent graft reinfection with HCV;
- or who have undergone liver transplantation and have aggressive, recurrent HCV infection resulting in progressive and worsening liver disease and are at high risk of death or decompensated liver failure within 12 months if left untreated.

I documenti prodotti in Europa da aprile a giugno 2014

HAS
HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE
Avis
14 mai 2014

SOVALDI 400 mg, comprimés pelliculés
Boîte de 28 (CIP : 34009 277 070 7 0)

Laboratoire Gilead Sciences

DCI	Sofosbuvir
Code ATC (année)	J05A (antiviraux à action directe)
Motif de l'examen	Inscription
Listes concernées	Sécurité Sociale (CSS L.162-17) Collectivités (CSP L.5123-2)
Indication concernée	« Sofosbuvir est indiqué en association à d'autres médicaments dans le traitement de l'hépatite C chronique chez l'adulte ».

Cosa è successo in Francia

A **settembre 2013** sofosbuvir è stato oggetto di una Autorisation Temporaire d'Utilisation (ATU) che lo concedeva a:

- pazienti in attesa di trapianto
- pazienti trapiantati con reinfezione da HCV aggressiva ed una attesa di vita (senza trattamento) < 12 mesi.

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Francia:
le raccomandazioni di HAS

14 Maggio 2014

Selon le rapport DHUMEAUX, il est d'ores et déjà souhaitable de proposer le traitement par sofosbuvir en priorité à tous les patients dont la maladie hépatique est au stade de fibrose F3 ou F4. Les patients au stade de fibrose F2 devraient bénéficier également de nouveaux traitements dans des délais courts. Pour les patients F0 ou F1 en fonction de l'évolution de la maladie, souvent très lente durant de nombreuses années, autorisant le clinicien à surseoir à la prescription dans l'attente d'une clarification des stratégies thérapeutiques, le traitement pourrait être différé.

Il est aussi recommandé de traiter certaines populations particulières, indépendamment du degré de fibrose, tels les patients en attente de transplantation d'organe, les femmes ayant un désir de grossesse, les usagers de drogues, les patients co-infectés par le VIH et les personnes détenues ainsi que les patients présentant des manifestations extra-hépatiques du virus de l'hépatite C.

Lettori: n.d.
Diffusione: n.d.
Les Echos
Dir. Resp.: Nicolas Barré
09-LUG-2014
da pag. 14

Hépatite C : un produit miracle relance le débat sur le prix des médicaments

- La société américaine Gilead négocie en France le prix de son traitement vendu 84.000 dollars aux Etats-Unis.
- Cet antiviral, bien toléré, guérit 90 % des patients, mais pose la question de sa prise en charge financière.

PHARMACIE

Catherine Ducruet
cducruet@lesechos.fr

C'est un choix cornélien pour le gouvernement. L'hépatite C est un problème majeur de santé publique avec plus de 3.000 décès chaque année. Mais il n'est pas sûr que tous les patients qui en souffrent pourront être traités avec le Sovaldi, le nouveau médicament miracle de la biotech américaine Gilead.

La société négocie, actuellement, le prix de remboursement de son produit, mais ses exigences, en cohérence avec les prix pratiqués aux Etats-Unis (84.000 dollars le traitement de douze semaines) apparaissent à beaucoup comme exorbitantes.

Dans ce contexte tendu, la publication, lundi, de la lettre adressée par le rapporteur du projet de loi de Finances sur la Sécurité sociale, le député PS, Gérard Bapt, au président de la filiale française de Gilead, Michel Jolly, a fait l'effet d'un pavé dans la mare. Gérard Bapt y épingle le prix actuel du médicament, disponible sous autorisation temporaire d'utilisation (ATU) à 56.000 euros pour douze semaines

teur de l'Agence nationale de recherche contre le sida et les hépatites, Jean-François Delfraissy. En revanche, Gérard Bapt ne mentionne pas les coûts de développement qui sont décisifs dans la détermination de la valeur du produit. Une étude de 2012 de Thomson Reuters sur les performances des groupes pharmaceutiques en matière d'efficacité de la R&D montrait que le coût moyen de développement d'un produit chez Amgen, seule société de biotechnologie à figurer dans le classement, dépassait les 3 milliards.

Mais même en conservant cet ordre de grandeur, le prix semble difficile à justifier car, dès cette année, les ventes de Sovaldi devraient atteindre 3 milliards de dollars aux Etats-Unis. Et on s'attendrait à 11 milliards de dollars l'année prochaine. Toutefois, en 2016, Gilead devrait enregistrer un recul dû, moins à l'apparition de concurrents, qu'à une régression du nombre de patients potentiels, sachant que le traitement guérit plus de 90 % d'entre eux.

Dans cette bataille sur les prix, il ne faut pas, en effet, oublier la révolution que le Sovaldi représente pour les patients. Jusqu'en 2011, le traitement de l'hépatite C combiné pour la plupart des souches d'hépatite C, il peut être pris sans interféron, et qu'une autre molécule actuellement en cours d'enregistrement, prise en association, permettra bientôt aux malades porteur de la souche de génotype 1, où il est encore recommandé, de s'en affranchir complètement. La HAS a d'ailleurs chiffré à 2 (sur une échelle de 1 à 5) l'amélioration du service médical rendu, prise en compte dans la détermination du prix tout en s'interrogeant « *sur la justification et la construction du prix revendiqué par l'industriel* ».

Une autre approche de la valeur du produit consiste à comparer le prix du traitement par Sovaldi aux économies qu'il permet de réaliser sachant que de 15 à 20 % des patients atteints d'hépatite C vont développer une cirrhose ou un cancer du foie nécessitant des greffes ou des traitements anticancéreux prohibitifs. Vu sous cet angle, le prix est sans doute moins aberrant. A condition bien sûr que les patients soient vraiment guéris. Ce qu'il est encore impossible d'affirmer puisqu'on ne dispose pas de suffisamment de recul dans le temps. ■

3.000 décès par an en France

Scottish Medicines Consortium

Providing advice about the status of all newly licensed medicines

NHS SCOTLAND

www.scottishmedicines.org.uk

Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

sofosbuvir 400mg tablet (Sovaldi®) SMC No. (964/14)

Gilead Sciences Ltd.

09 May 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drugs and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

Scozia:
le raccomandazioni di Scottish Medicines Consortium (SMC)

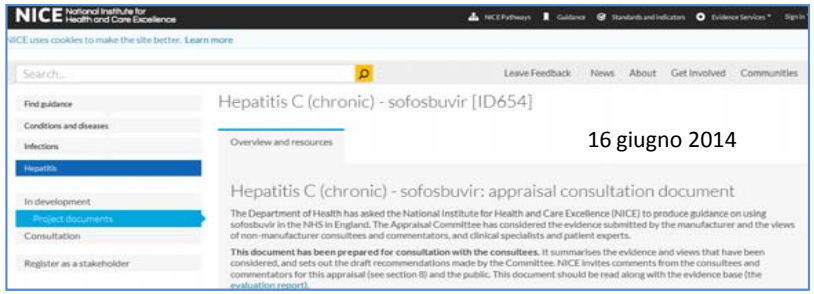
14 Maggio 2014

SMC restriction: Sofosbuvir is accepted for use in patients with genotypes 1 to 6.

Use in treatment-**naive patients with genotype 2 is restricted to those who are ineligible for, or are unable to tolerate, peginterferon alfa.**

Use of the 24-week **interferon-free regimen of sofosbuvir in combination with ribavirin in patients with genotype 3 is restricted to those who are ineligible for, or are unable to tolerate, peginterferon alfa.**

Sofosbuvir in combination with ribavirin, or peginterferon plus ribavirin, produced sustained virological suppression in patients with all genotypes of hepatitis C. It is the first medicine licensed for use in interferon-free regimens and may be associated with improved tolerability compared to standard interferon-based regimens.



16 giugno 2014

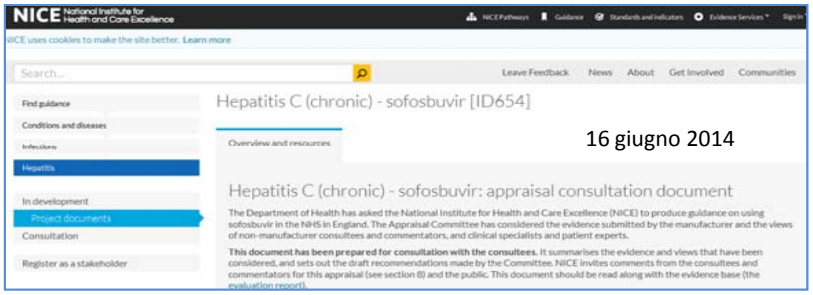
Cosa è successo in Gran Bretagna (NICE)

La consultazione è stata chiusa il **4 luglio 2014**

Il "Second Appraisal Committee meeting" avrà luogo il **15 Luglio 2014**

"The available evidence shows that sofosbuvir is an effective treatment for chronic hepatitis C in certain patients. However, evidence is lacking for some subgroups of patients with chronic hepatitis C, and there are also substantial uncertainties in the evidence base presented by the manufacturer.

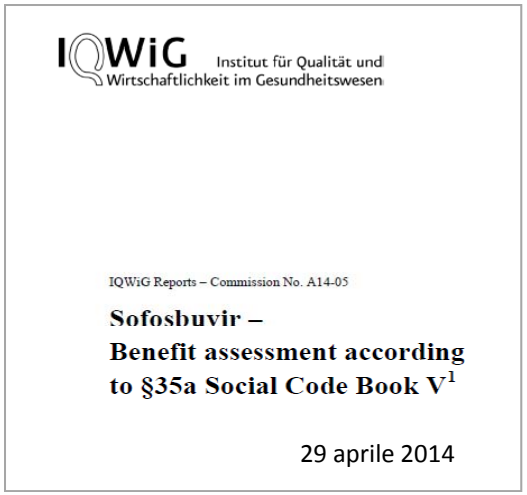
The Committee has therefore requested further information from the manufacturer before it can decide whether sofosbuvir is a cost-effective use of NHS resources."



Alcuni commenti del NICE

The ERG reviewed the clinical evidence in the manufacturer's submission. It considered that the manufacturer's interpretation of the clinical evidence was overall justified and unbiased. However, the ERG cautioned that most of the evidence provided did not directly address the decision problem, because of the lack of head-to-head studies against current standard of care comparators.
In addition, it highlighted that no studies were included that examined the efficacy of sofosbuvir within its licensed indication for treatment-experienced people with genotype 1 HCV. The ERG also noted that some of the evidence supporting the treatment regimens licensed for use in people with genotype 3 HCV (from VALENCE) should be interpreted with caution because randomisation was broken during the study, and some people were switched from 12 to 24 weeks of treatment with sofosbuvir plus ribavirin.

…….. Overall, the ERG was satisfied that the evidence indicated that treatment with sofosbuvir-based regimens was generally well tolerated and led to fewer adverse events than treatment with peginterferon alfa and ribavirin.



Cosa è successo in Germania

29 Aprile 2014

L' Institute for Quality and Efficiency in Health Care (IQWiG), sulla base delle evidenze scientifiche disponibili, ha dichiarato che non esistono i presupposti per attribuire al sofosbuvir un generico valore terapeutico aggiunto rispetto alle terapie disponibili (interferone+ ribavirina), soprattutto in relazione ai dati disponibili per i diversi genotipi virali (carenti per quanto riguarda pazienti con infezione da genotipo 1, 3, 5, 6).

Valutazioni del documento IQWIG (1)

Table 6: Research questions of the benefit assessment of sofosbuvir

Research question	Therapeutic indication CHC	Approved treatment regimen	ACT
1	Genotype 1, treatment-naive without cirrhosis, and treatment-experienced with and without cirrhosis	SOF + PEG + RBV	PEG + RBV or[a] BOC + PEG + RBV or TVR + PEG + RBV
1b	Genotype 1, treatment-naive patients with cirrhosis	SOF + PEG + RBV	PEG + RBV
2	Genotype 2	SOF + RBV	PEG + RBV
3	Genotype 3	SOF + PEG + RBV or SOF + RBV	PEG + RBV
4	Genotype 4	SOF + PEG + RBV	PEG + RBV
5	Genotype 5 or 6	SOF + PEG + RBV	PEG + RBV
6	Patients with HIV coinfection (genotype 1–6)	According to genotype	PEG + RBV

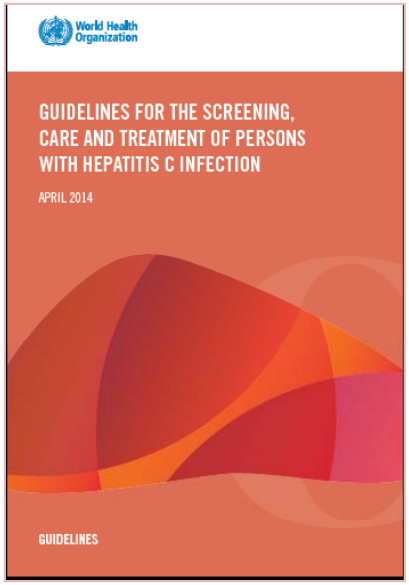
a: Under consideration of the necessity of using triple therapy when favourable prognostic factors are present.

ACT: appropriate comparator therapy; BOC: boceprevir; CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; SOF: sofosbuvir; TVR: telaprevir

Valutazioni del documento IQWIG (2)

Table 4: Sofosbuvir – extent and probability of added benefit

Research question	Patient group with CHC	ACT[a]	Extent and probability of added benefit
1	Genotype 1, treatment-naive without cirrhosis, and treatment-experienced with and without cirrhosis	PEG + RBV or[b] **BOC + PEG + RBV or** **TVR + PEG + RBV**	Added benefit not proven
1b	Genotype 1, treatment-naive patients with cirrhosis	PEG + RBV	Added benefit not proven
2	Genotype 2	PEG + RBV	Treatment-naive patients: indication of added benefit of sofosbuvir (extent "non-quantifiable")
			Treatment-experienced patients: added benefit not proven
3	Genotype 3	PEG + RBV	Added benefit not proven
4	Genotype 4	PEG + RBV	Added benefit not proven
5	Genotype 5 or 6	PEG + RBV	Added benefit not proven
6	Patients with HIV coinfection (genotype 1–6)	PEG + RBV	Added benefit not proven



La LG dell'OMS

Aprile 2014

At the time of writing (December 2013), six drugs are licensed for the treatment of HCV – standard interferon (IFN) or pegylated interferon alpha (PEG-IFN), ribavirin (RBV), the protease inhibitors (PIs) boceprevir, simeprevir and telaprevir, and the nucleotide analog polymerase inhibitor sofosbuvir.

The limitations of treatment include high cost, the need for sophisticated laboratory tests and trained clinicians, as well as the limited efficacy and high toxicity of some of the medicines.

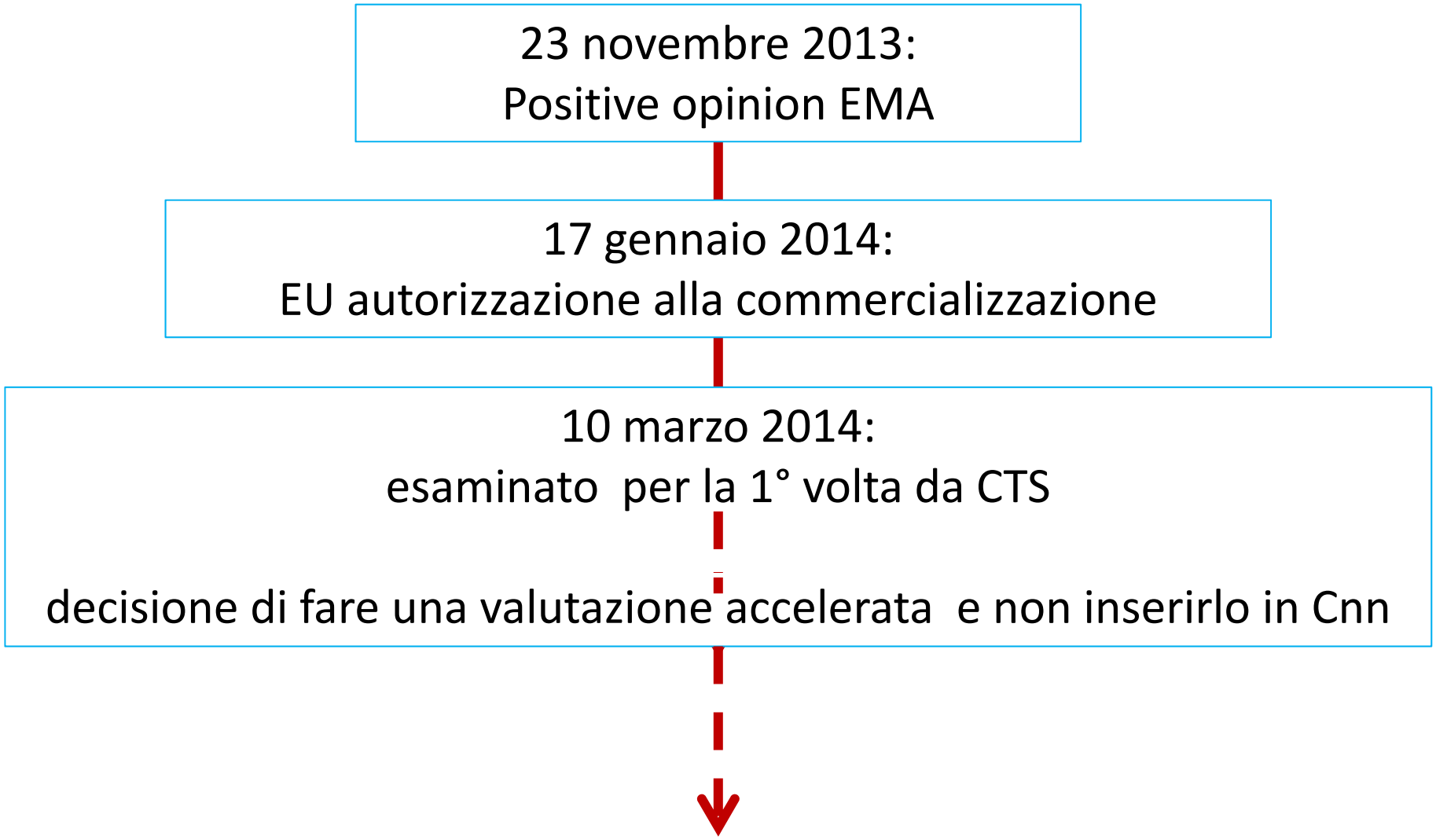
It is anticipated that the number of medicines for the treatment of HCV will expand rapidly over the coming years, and WHO plans to periodically update these guidelines to include newly licensed drugs.

Elementi comuni ai documenti europei

Tutti i documenti:

- contengono dati epidemiologici (frequenza dell'infezione, prevalenza dei genotipi …..)
- presentano un'analisi dettagliata/critica delle prove di efficacia in funzione del:
  - *genotipo,*
  - *quadro istologico*
  - *caratteristiche del paziente*
  - *rispetto all'attuale standard di cura*
- presentano una strategia che prevede la definizione di priorità d'uso
- ribadiscono che l'argomento è in rapida evoluzione
- considerano i costi.

Percorso del sofosbuvir in Italia



Comunicato n. 367

11 giugno 2014

Agenzia Italiana del Farmaco

AIFA

Incontro CPR AIFA - Gilead per processo negoziazione terapia Epatite C

In occasione della riunione straordinaria del Comitato Prezzi e Rimborso di AIFA del 9 giugno c.a., il Comitato, come previsto nell'accordo iniziale, ha preso atto della richiesta di Gilead di sospendere la negoziazione di Sofosbuvir per un periodo di 30 giorni al fine di definire i dettagli dell'accordo.

Durante questo periodo AIFA e Gilead hanno previsto una soluzione per fornire da subito il farmaco ai pazienti affetti da epatite C nei casi più urgenti [ovvero pazienti con recidiva severa di epatite dopo trapianto di fegato (epatite fibrosante colestatica o epatite cronica con grado di fibrosi >F2 METAVIR) oppure pazienti con cirrosi scompensata in lista per trapianto epatico (MELD < 25)].

Epatite C - Procedura negoziale Sovaldi (sofosbuvir) e accesso gratuito al farmaco

09/07/2014

L'Agenzia Italiana del Farmaco (AIFA) comunica che la ditta Gilead non ha ritenuto possibile presentarsi alla riunione del Comitato Prezzi e Rimborso indetta per lo scorso 4 luglio al fine di concludere la procedura negoziale del prodotto Sovaldi (sofosbuvir) ed ha chiesto una proroga fino al 29 settembre 2014.

Indipendentemente dall'attività di negoziazione del prezzo del medicinale, è già attiva una procedura di fornitura gratuita del farmaco, per rendere disponibile da subito il medicinale ai pazienti affetti da epatite C nei casi più urgenti, quali quelli di pazienti con:
recidiva severa di epatite dopo trapianto di fegato (epatite fibrosante colestatica o epatite cronica con grado di fibrosi >F2 METAVIR)
cirrosi scompensata in lista per trapianto epatico (MELD < 25).
Il medicinale verrà fornito secondo le modalità previste dal D.M. 08/05/2003 (Uso Compassionevole) e a tal proposito la Gilead ha attivato un indirizzo di posta elettronica **epatitec@gilead.com** a cui i soli medici potranno inoltrare le richieste per i pazienti che rientrino nei criteri indicati.

In tale occasione si ribadisce, vista l'urgenza del trattamento di tali pazienti, l'importanza da parte degli operatori sanitari coinvolti ed in particolare dei Comitati Etici, di valutare tempestivamente l'inserimento degli stessi nel programma di accesso gratuito al farmaco.

In conclusione

è **urgente,** anche per il nostro Paese:

- definire una strategia per i pazienti più gravi
- produrre un documento che definisca per i farmaci disponibili le raccomandazioni d'uso e le priorità di accesso considerando
  - le caratteristiche della malattia e la sua evoluzione clinica
  - l'ampia disponibilità (a breve termine) di farmaci efficaci e che consentiranno terapie più tollerabili e di più breve durata
  - la sostenibilità economica.