National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sofosbuvir for treating chronic hepatitis C [ID654]

You are asked to check the ERG report from Southampton Health Technology Assessment Centre (SHTAC) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Wednesday 16 April 2014** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Incorrect licensed indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Statements relating to the licensed indication for sofosbuvir are incorrect and/or misleading. On Page 7, Summary the report states: *Sofosbuvir is licensed for use in combination with ribavirin with or without peginterferon alfa-2a or peginterferon alfa-2b, for either 12 or 24 weeks of therapy depending upon the patient's HCV genotype and treatment history. Due to the licensed indications for sofosbuvir being HCV-genotype-specific, some of the patient groups listed above have more than one licensed sofosbuvir regimen.* On page 15, Section 2.3, Intervention the report states: *The intervention, sofosbuvir (SOF), is licensed for the treatment of chronic hepatitis C when administered together with ribavirin (RBV) (dual therapy) or when administered together with RBV and peginterferon-alfa (triple therapy).* *On page 20, Section 3.1.3 the reports states:* *'...in Table 1 according to which of the licensed indications they inform i.e. the specific combinations of HCV genotype*	The text should be amended as follows: Page 7 *Sofosbuvir is ~~licensed for use in combination with ribavirin with or without peginterferon alfa-2a or peginterferon alfa-2b, for either 12 or 24 weeks of therapy depending upon the patient's HCV genotype and treatment history. Due to the licensed indications for sofosbuvir being HCV-genotype-specific, some of the patient groups listed above have more than one licensed sofosbuvir regimen~~. indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults. The average length of a course of treatment is 12 or 24 weeks according to genotype and status with regards to interferon.* Page 15 *The intervention, sofosbuvir (SOF), is ~~licensed for the treatment of chronic hepatitis C when~~ indicated in combination with other medicinal products for the treatment of chronic*	The current text is incorrect in: • not stating the actual licensed indication and • stating '*due to the licensed indications'* which suggests that there is more than one indication. This is not the case as there is one indication with different dosing regimens. The suggested amendments highlight the correct licensed indication and specify that the recommended treatment regimens for sofosbuvir are based on genotype, previous treatment history and suitability/unsuitability to interferon treatment.	The ERG does not believe this is a factual inaccuracy; however, as the manufacturer suggests the choice of wording could be misleading we have reworded as follows: ERG rewording on page 7: *Sofosbuvir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adults. The average length of a course of treatment is 12 or 24 weeks according to patients' HCV genotype and history of prior treatment with interferon.* ERG rewording on page 15: *The intervention, sofosbuvir (SOF), is indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adults. Sofosbuvir can be administered together with ribavirin (RBV) (dual therapy) or together with RBV and peginterferon-alfa (triple therapy).* ERG rewording on page 20: *…in Table 1 according to which of the licensed regimens of sofosbuvir*

and patients' treatment history (naive or experienced)'	*hepatitis C (CHC) in adults. Sofosbuvir can be administered together with ribavirin (RBV) (dual therapy) or when administered together with RBV and peginterferon-alfa (triple therapy).* *Page 20* *'...in Table 1 according to ~~which of the licensed indications they inform i.e. the specific combinations of~~ HCV genotype and patients' treatment history (naive or experienced)'*		*they inform, i.e. the specific combinations of HCV genotype and patients' treatment history (naive or experienced).*

Issue 2 VALENCE – Placebo treatment group

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27, 3.1.4 Description and critique of the approach to validity assessment The ERG report states: *'The VALENCE trial was therefore unblinded and genotype 3 patients were given 24 weeks of therapy instead of 12 weeks As a consequence of unblinding, placebo patients were discontinued after a median of 8 weeks and offered an alternative treatment protocol (the manufacturer provided no details in their clarifications about what treatment was received). The ERG therefore considers that any comparisons made against the*	Sentence to be revised as follows: *'The VALENCE trial was therefore unblinded and genotype 3 patients were given 24 weeks of therapy instead of 12 weeks As a consequence of unblinding, placebo patients were discontinued after a median of 8 weeks and offered treatment with SOF+RBV under a separate protocol (Study GS-US-334-0109 Rollover Study)' an alternative treatment protocol ~~(the~~*	Details of the treatment received by placebo patients were provided within Table 10 of the Gilead submission: *'The initial treatment duration for all patients was 12 weeks but following data from FUSION which indicated that patients with HCV GT3 would benefit from extending treatment beyond 12 weeks, VALENCE was amended to allow 24 weeks of treatment for the GT3 subgroup. All GT2 patients randomised to active treatment continued to receive SOF+RBV for 12 weeks and all*	Not a factual inaccuracy. No action required.

placebo group in this trial should be interpreted with caution.'	*~~manufacturer provided no details in their clarifications about what treatment was received). The ERG therefore considers that any comparisons made against the placebo group in this trial should be interpreted with caution.~~'*	*placebo recipients were discontinued from the study and offered treatment with SOF+RBV under a separate protocol (Study GS-US-334-0109 Rollover Study)'* Whilst not a factual inaccuracy we would also like to clarify that at the time of the amendment unblinding the study, 11 GT3 patients had already completed 12 weeks of treatment; the remaining 250 GT3 patients were treated for 24 weeks. The 11 GT3 patients who received 12 weeks of SOF + RBV (unlicensed treatment duration) were excluded from the final efficacy analyses because of the different treatment duration. The primary endpoint of SVR12 was not influenced by the discontinuation of the placebo arm as no patients, as expected, in this group achieved SVR12. Therefore it is incorrect to state that comparisons against the placebo group need to be interpreted with caution.	

Issue 3 HCV/HIV Coinfection – SVR rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, section 4.2.4, clinical	*'The MS argues that SVRs are similar between*	The statement 'The MS argues,' implies that no evidence was available supporting the justification that SVR rates for HCV mono-infected patients and HCV/HIV co-infected patients are comparable. Within the submission	Not a factual inaccuracy. No action required.

effectiveness. The ERG report states: *'The MS argues that SVRs are similar between mono-infected and co-infected populations (MS p. 168) and uses this as justification to not split out results for the co-infected subgroup in the main economic analysis'.*	*mono-infected and co-infected populations (MS p. 168) and uses this as justification to not split out results for the co-infected subgroup in the main economic analysis*. Whilst the MS did not provide a comparison of the SVRs for these two populations, the data presented within the individual results sections supports the justification that the rates are similar.	document, data is presented for these two populations and whilst a tabulation comparing SVR rates was not included, the data presented within the individual results sections supports the justification that the rates are similar. The preferred regimen for HCV/HIV co-infected patients is SOF + PEG + RBV (12 weeks) unless patients are unsuitable to interferon. Table 1 details the SVR rates for HCV/HIV co-infected patients and HCV mono-infected patients treated with 12 or 24 weeks of SOF + RBV within each genotype as per the submission document. SVR rates for HCV mono-infected patients vs HCV/HIV co-infected patients were 68% vs 76% (GT1 treated with SOF + RBV x 24 weeks), 93% vs. 88% (GT2 treatment naïve, treated with SOF + RBV x 12 weeks), 56% vs. 67% (GT3 treatment naïve, treated with SOF + RBV x 12 weeks), and 85% vs. 92% (GT3 treatment experienced, treated with SOF + RBV x 24 weeks), respectively. The recently published 2014 EASL (European Association of the Study of the Liver) Recommendations on the Treatment of Hepatitis C[9] also highlight : • Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection **(Recommendation A1)** • The same treatment regimens can be used in HIV-coinfected patients as in patients without HIV infection, as the virological results of therapy are identical **(Recommendation A1)** • No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs **(Recommendation A2)** The MS highlights that the preferred regimen for the HCV/HIV co-infected population should be SOF + PEG + RBV for 12 weeks as per the mono-infected populations. Since the submission, additional data from study 1910[6] (as noted within the original MS submission section 1.6) has become available and we have provided this for information. SVR rates for HCV mono-infected patients vs HCV/HIV co-infected patients were 91%, reinforcing that similar response rates were seen in HCV/HIV co-infected	

patients as HCV mono-infected patients treated with SOF + PEG + RBV in GT1 patients. Please note that with agreement, published details of study 1910 have been provided to NICE.

Table 1

Monoinfection/Coinfection Trial	Genotype	TN/TE	Regimen	Duration (weeks)	Number of patients achieving SVR12	SVR12 Response (%)
PHOTON-1[1]	GT1	TN	SOF/RBV	24	87/114	76
SPARE[2]	GT1	TN	SOF/RBV	24	17/25	68
PHOTON-1[1]	GT2	TN	SOF/RBV	12	23/26	88
VALENCE[3]	GT2	TN	SOF/RBV	12	68/73	93
PHOTON-1[1]	GT3	TN	SOF/RBV	12	28/42	67
FISSION[4]	GT3	TN	SOF/RBV	12	102/183	56
PHOTON-1[1]	GT3	TE	SOF/RBV	24	12/13	92
VALENCE[5]	GT3	TE	SOF/RBV	24	212/250	85
STUDY 1910[6]	GT1	TN	SOF/PEG/RBV	12	21/23	91
NEUTRINO[4]	GT1	TN	SOF/PEG/RBV	12	296/327	91

Issue 4 SVR rates – model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12, weaknesses and areas of uncertainty. The ERG report states *'The economic model structure is modified from a structure used in previous HTAs for HCV and replaces 'mild', 'moderate', and 'severe' cirrhosis health states with 'non-cirrhotic' and 'cirrhotic'. As a consequence SVRs are required for each of these health states but there is a paucity of data in the literature to fulfil the requirements of the model. The clinical efficacy data may therefore not be robust.'* Page 101, section 4.4, summary The ERG report states: *'The model replaces the 'mild', 'moderate' and 'severe' cirrhosis starting health states of previous models with two health states, non-cirrhotic and cirrhotic. Consequently the model requires estimates of proportion achieving SVR for each of these health states but these data are less common in the literature than data for the 'mild', 'moderate' and 'severe' health states. The clinical efficacy data used in the model are thus in many cases not robust. '*	Page 12, weaknesses and areas of uncertainty. *'The economic model structure is modified from a structure used in previous HTAs for HCV and replaces 'mild', 'moderate', and 'severe' cirrhosis health states with 'non-cirrhotic' and 'cirrhotic'. As a consequence SVRs are required for each of these health states ~~but there is a paucity of data in the literature to fulfil the requirements of the model. The clinical efficacy data may therefore not be robust~~.'* Page 101, section 4.4, summary *'The model replaces the 'mild', 'moderate' and 'severe' cirrhosis starting health states of previous models with two health states, non-cirrhotic and cirrhotic. Consequently the model requires estimates of proportion achieving SVR for each of these health states ~~but these data are less common in the literature than data for the 'mild', 'moderate' and 'severe' health states. The clinical efficacy data used in the model are thus in~~*	The current text is misleading. The choice of model structure does not impact upon the robustness of the clinical efficacy data selected to populate the model, as in most instances SVR data for non-cirrhotic and cirrhotic cohorts were available from the clinical literature. Where data was scarce (e.g.GT2/3 treatment experienced) we took a conservative approach to select the inputs from the available data. Our selection process was as follows: • Non-cirrhotic SVR rates were when available based on the same definition as the ones used in the sofosbuvir trial, i.e. METAVIR F0-F3. Cirrhotic SVR rates were based, when available on the same definition as the one used in the sofosbuvir trials, i.e. METAVIR F4. • For GT1 treatment naïve, (telaprevir and boceprevir) we used results from their phase III trial programmes, i.e. ADVANCE and LAWITZ	Not a factual inaccuracy; however, the choice of wording could be misleading. The ERG consider there is a paucity of good quality data, particularly in some genotype subgroups as indicated here in the manufacturer's justification for the proposed amendment and in the MS discussion of the MTC (page 177) where it states 'this level of information was scarcely reported in the literature'. We have reworded as follows: ERG rewording on page 12: *The economic model structure is modified from a structure used in previous HTAs for HCV and replaces 'mild', 'moderate', and 'severe' cirrhosis health states with 'non-cirrhotic' and 'cirrhotic'. As a consequence SVRs are required for each of these health states but in some HCV genotype subgroups there is a paucity of good quality data in the literature to fulfil the requirements of the model. The*

	~~*many cases not robust.*~~ ‘	to inform the SVR rates. In their respective publications, they directly provided the SVR rates by METAVIR score and we used this to populate the SVR rates for cirrhotic and non-cirrhotic in our model. • For dual combination of PEGINF2a and ribavirin for 48 weeks, we used results from the IDEAL trial, defining non-cirrhotic SVR rates on F0-F2 patients and cirrhotic SVR rates on F3-F4 patients. We believe this reflects a conservative approach in favour of PEG + RBV dual therapy when compared to sofosbuvir. • For GT2 and GT3 treatment naïve, we used the results from the FISSION trial which directly compared sofosbuvir and PEG+RBV for 24 weeks. • For GT2 and GT3 treatment experienced, we were limited by the lack of data available in the literature to find inputs for PEG+RBV for 48 weeks. This would also have been the case had we used a different (mild/moderate) model structure. • For GT4/5/6, we used Manns	*clinical efficacy data may therefore not be robust* ERG rewording on page 101: *The model replaces the ‘mild’, ‘moderate’ and ‘severe’ cirrhosis starting health states of previous models with two health states, non-cirrhotic and cirrhotic. Consequently the model requires estimates of proportion achieving SVR for each of these health states but in some genotype subgroups there are limited good quality data available and therefore the clinical efficacy data used in the model may not be robust.*

		et al. 2001 where SVR rates were reported split by genotype and degree of fibrosis. Our estimates were based on the assumption that the increase in SVR between fibrosis/cirrhosis and no/minimal fibrosis were identical across genotypes 1/2/3 and 4/5/6.	

Issue 5 External Model Validation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12, weaknesses and areas of uncertainty. The ERG report states: *'The model is not well validated against external data. This is particularly the case with the comparison with boceprevir+PEG2b+RBV where the MS model outcomes do not agree with previously presented results for this treatment.* '	*'The model is not well validated against ~~external data. This is particularly the case with~~ the comparison with boceprevir+PEG2b+RBV where the MS model outcomes do not agree with previously presented results for this treatment.'*	The statement that the model has not been externally validated is incorrect. The model was externally validated based on recent NICE submissions employing similar model structures which are more reflective of UK clinical practice (e.g. telaprevir). In the ERG report, attempts at validating the new structure were made by comparing current results for telaprevir and boceprevir with reported results from their submissions. It was found that results were similar for telaprevir but not with boceprevir. We would like to highlight that the slight	Not a factual inaccuracy. No action required.

		differences observed between the Gilead estimates for telaprevir and the previously published results could be explained as follows: • The two model structures are similar with the only difference being that in the Gilead model mild and moderate were pooled together • The transition probabilities and utilities utilised were similar • However in the telaprevir model, the naïve population results were based on the pooled estimates of three separate cohorts. These three cohorts differed in terms of the age where patients would start treatment and would have a different proportion of mild, moderate and cirrhotic patients. Regarding boceprevir, the results are inconclusive for the following reasons: • The model structure used in the boceprevir submission is different from the one used by sofosbuvir, telaprevir or Hartwell et al 2011. Patients could progress from F0 to F1, F1 to F2, F2 to F3 and F3 to F4.	

		• The boceprevir model had separate inputs in terms of distribution, SVR rates and resource use • The transition probabilities for the first five health states (F0, F1, F2, F3 and F4) were based on a meta-regression published by Thein et al. 2008[7] after making assumptions with regards to the patient characteristics (e.g. age).	

Issue 6 VALENCE – Clarification of licensed regimen

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40, Section 3.3, HCV genotype 2/3 combined treatment experienced and treatment naive. The ERG report states: *The SOF+RBV 12-week regimen resulted in SVR12 rates of 78% (95% CI 72-83%; N=207) in mixed genotype 2/3 patients (POSITRON), [redacted]) genotype 2 patients (VALENCE) and [redacted]) in genotype 3 patients (VALENCE), although it should be noted that the sample size for genotype 3 was relatively small.*	Text to be added specifying that the 12 week regimen is not the licensed regimen for GT3 *The SOF+RBV 12-week regimen resulted in SVR12 rates of 78% (95% CI 72-83%; N=207) in mixed genotype 2/3 patients (POSITRON), [redacted]) genotype 2 patients (VALENCE) and [redacted]) in genotype 3 patients (VALENCE), although it should be noted that the sample size for genotype 3 was*	The 12 week regimen is not the licensed regimen for GT3 and the lack of clarification on this is an important issue. We understand that the focus of the ERG report should be on the licensed regimens only.	Not a factual inaccuracy; however, the ERG agrees that clarification that the 12-week regimen is not licensed for genotype 3 would be helpful. We have done this as follows: <u>ERG rewording on page 40</u>: The SOF+RBV 12-week regimen resulted in SVR12 rates of 78% (95% CI 72-83%; N=207) in mixed genotype 2/3 patients (POSITRON), [redacted]) in genotype 2 patients (VALENCE)

	relatively small. <u>It should also be noted that the 12 week regimen is not licensed for GT3.</u>		and [redacted]) in genotype 3 patients (VALENCE). *It should be noted that the sample size for genotype 3 was relatively small and the 12-week regimen is not licensed for this genotype.* Although not pointed out as inaccuracies by the manufacturer, for consistency with our response to the manufacturer's comment here we have also updated the SVR12 ranges reported so they are only for licensed regimens (previously ranges referred to all reported SVRs). The changes are: <u>Page 8, 2nd paragraph</u>: *SVR12 rates in sofosbuvir regimens of the included studies ranged from 50% to 100%, depending upon the regimen, duration of therapy, and treatment history of the patients* <u>Page 8, 4th bullet point</u>: *HCV genotype 3 subgroup: SVR12 ranged from [redacted]% to 100% (in studies on treatment experienced and treatment naive patients respectively).*

			Page 52, 4th paragraph: *SVR12 frequencies in sofosbuvir regimens of the included studies ranged from 50% to 100%, depending upon the sofosbuvir regimen, duration of therapy, and treatment history of the patients.*

Issue 7 Labelling of trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21, Section 3.1.3, Identified studies The ERG comment that the single-cohort NEUTRINO is incorrectly labelled as an RCT is misleading. A statement is also made that within the MS submission four of the phase 2 studies are not identified as RCTs.	Replace current text with 'Within the Executive Summary the MS includes a typographical error and incorrectly states that NEUTRINO is randomised' and delete reference to the four phase 2 studies	Within the main body of the submission NEUTRINO is referred to correctly. There is an error in the Executive Summary. The descriptions of the four phase 2 RCTs studies make reference to randomisation.	Not a factual inaccuracy. No action required.

Issue 8 Transition probability SVR Cirrhotic to HCC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97, section 4.3, additional work undertaken by the ERG.	*'The manufacturer's clarification letter does not supply details of the calculation of this probability from*	The transition probability used by the MS in response to the ERG clarification request is assumed correct	Not a factual inaccuracy. No action required.

The ERG report states: *'The manufacturer's clarification letter does not supply details of the calculation of this probability from figures given in Cardoso and colleagues[72] and the ERG was unable to reproduce the value of 0.005. The rate of HCC given SVR supplied in Cardoso and colleagues (table 2) is 1.24 per 100 person years[72] which by ERG calculations corresponds to a transition probability of 0.0123 per year.'*	*figures given in Cardoso and colleagues[72] and the ERG was unable to reproduce the value of 0.005. ~~The rate of HCC given SVR supplied in Cardoso and colleagues (table 2) is 1.24 per 100 person years[72] which by ERG calculations corresponds to a transition probability of 0.0123 per year.~~*	based on published literature according to Chhatwal et al. 2013[8] based on Cardoso et al. 2010.	Chhatwal et al. 2013 is not cited in the manufacturer's clarification letter.

Issue 9 Cirrhotic SVR rates (Roberts et al., 2009)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71, section 4.2.4, clinical effectiveness. The ERG report states: *In the Roberts and colleagues[51] trial the SVRs were 55% and 24% for the two groups respectively.*	*In the Roberts and colleagues[51] trial the SVRs were 55% and ~~24%~~ 6% for the two groups respectively*	The current statement is incorrect. The cirrhotic SVR rate of 24% (Roberts et al., 2009) stated in the ERG report are for bridging fibrosis and cirrhosis (F3-F4) and not cirrhosis (F4) as reported in our model. Roberts reported 6% for METAVIR score equal to F4. The results from the additional ERG analysis [p94], table 31] are based on the incorrect SVR rate which would result in different ICERs to those based on a 6%	We agree that the Roberts and colleagues SVR for the F4 health state is 6%. The MS used McHutchinson et al data for the cirrhosis state which was based on F3 and F4 and the ERG therefore used F3 and F4 data from Roberts (and Hadziyannis et al) for consistency with the manufacturer. ERG amendment, page 71: *In the HCV genotype 1 treatment naive interferon eligible group*

		SVR.	*the source of data for the PEG2a + RBV treatment was taken from McHutchinson and colleagues.[8] The estimates used by the manufacturer for the non-cirrhotic and cirrhotic groups taken from McHutchinson and colleagues[8] relate to METAVIR scores F0-2 and F3-4 respectively (bridging fibrosis/cirrhosis). In the appendix describing the MTC a variety of studies in this patient subgroup were reported, of which McHutchinson and colleagues is the largest and therefore likely to be the most reliable source of data (although the MS does not state that this was why McHutchinson and colleagues was chosen). However, the manufacturer's MTC searches identified two other large RCTs by Hadziyannis and colleagues[50] and Roberts and colleagues.[51] The ERG has checked these trials for the SVR in these subgroups and rates appear to be different from those of McHutchinson and colleagues.[8] To be consistent with the MS the ERG has used METAVIR F0-2 for non-cirrhosis and F3-4 for cirrhosis in this genotype subgroup. In the Hadziyannis and colleaguesl[50]*

			trial the SVR in a non-cirrhotic group was approximately 56% (estimated from a figure) and in a cirrhotic group was approximately 38%. In the Roberts and colleagues[51] trial the SVRs were 55% and 24% for the two groups respectively. However, in the Roberts and colleagues[51] trial SVRs for each METAVIR group were presented separately and therefore a calculation of the SVRs in METAVIR F0-3 and F4 can be extracted. These rates were 51% and 6% respectively. Alternative SVR estimates for PEG2a+RBV in an HCV genotype 1 treatment naive population are examined by the ERG in additional analyses given in section 4.3. An amendment has been made to the ERG report (page 93) to provide clarification that the F3 and F4 state were used for consistency with the manufacturer but that data for Roberts were available for F0-3 (SVR 51%) and F4 (SVR 6%) and this would have the effect of slightly reducing the ICER for SOF+PEG+RBV to replace

			PEG+RBV. ERG amendment, page 93: *The Roberts and colleagues51 PEG2a+RBV SVR estimates are associated with an ICER of £18,209 per QALY for SOF+PEG2a+RBV compared to PEG2a+RBV, again an increase compared to the base case (Table 31). Using F0-3 data for non-cirrhosis and F4 data for cirrhosis (see discussion in Section 4.2.3, p71) would have the effect of slightly reducing the ICER.With the Hadziyannis and colleagues PEG2a+RBV SVR estimates50 the ICER for SOF+PEG2a+RBV compared to PEG2a+RBV becomes £21,848 (Table 32), i.e. within this indication SOF+PEG-IFN-2a+RBV is no longer cost-effective compared to PEG2a+RBV at a WTP of £20,000 per QALY.*

References

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