Review of orphan treatments assessed by NICE and the SMC in the UK

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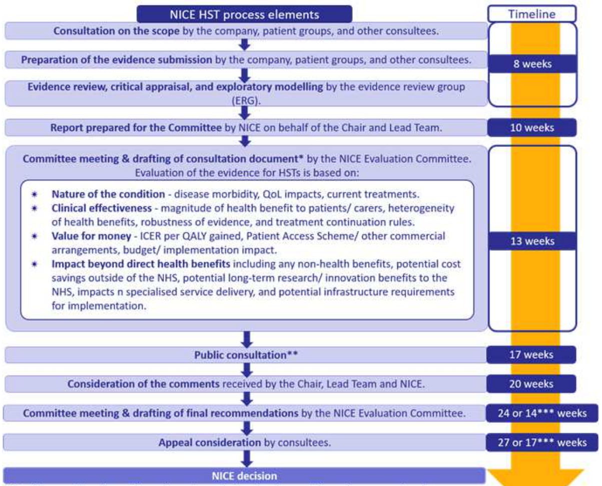
Introduction

- Health Technology Assessment (HTA) of new medicines is conducted to determine access for NHS patients in England and Scotland, however, the key drivers of these assessments (clinical– and cost-effectiveness) may not be consistent across HTA organisations, leading to disparities in treatment availability for patients.
- Treatments for diseases with a prevalence of ≤5 in 10,000 in the EU, which are life-threatening or severely disabling and have no satisfactory treatment available, are granted orphan designation by the European Medicines Agency (EMA)[1].
- In order to be considered for the NICE Highly Specialised Technology Programme (HSTP) or the SMC ultra-orphan process, a number of specialised criteria must be met (**Table 1**).
- Treatments for orphan diseases are subject to rigorous assessment processes to determine their availability within the NHS in England (NICE HST, see **Figure 1**) and Scotland (SMC ultra-orphan, see **Figure 2**).
- Medicines for orphan diseases that do not meet all of the NICE HST criteria are assessed via the Single Technology Appraisal (STA) process, and may be made available via programmes such as the Cancer Drugs Fund (CDF), which allows patients access to high-cost new cancer medicines under a Managed Access Agreement (MAA) and further enhances the clinical evidence base.

Table 1: Criteria for treatments to be considered as HST/ ultra-orphan

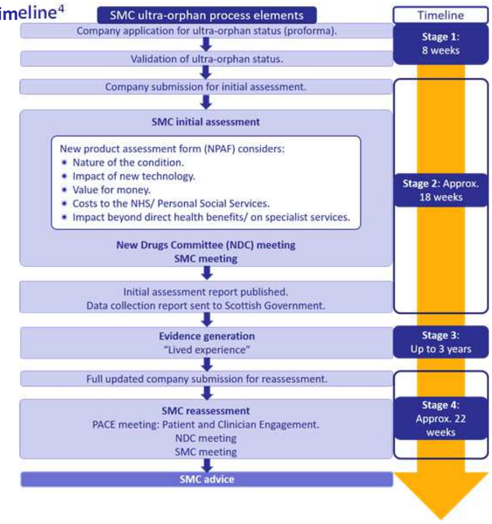
NICE[2]
The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS.
The target patient group is distinct for clinical reasons.
The condition is chronic and severely disabling.
The technology is expected to be used exclusively in the context of a highly specialised service.
The technology is likely to have a very high acquisition cost.
The technology has the potential for life long use.
The need for national commissioning of the technology is significant.
SMC[3]
The condition has a prevalence of 1 in 50,000 or less in Scotland.
The medicine has an EMA orphan designation for the condition and this is maintained at time of marketing authorisation.
The condition is chronic and severely disabling.
The condition requires highly specialised management.

Figure 1: Summary of NICE HST process elements and timeline[2]



*Positive opinion from the relevant regulatory body must have been received
**Marketing Authorisation must have been granted.
***Without public consultation.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life

Figure 2: Summary of SMC ultra-orphan process elements and timeline[4]



Objectives

- This research aimed to:
  - Review recent assessments of orphan and ultra-orphan drugs by NICE and the SMC.
  - Identify any disparities in availability of orphan drugs for NHS patients between England and Scotland.

Methods

- The EMA website was searched in August 2019 to identify orphan treatments authorised between 1st January 2018 and 1st September 2019.
- Treatments authorised by the EMA which were then subsequently assessed by NICE and SMC were reviewed for details surrounding the assessments and recommendations.

Results

Table 2: Summary of NICE and SMC recommendations for orphan treatments

Drug (Trade) name	Disease area	Date of EMA Marketing Authorisation	NICE recommendation (terms of recommendation)	SMC recommendation (assessment criteria)
Inotersen (TEGSEDI)	Hereditary transthyretin (hATTR) amyloidosis	05/07/2018	✓ HST (PAS)[5]	✓ (UO)[6]
Axicabtagene ciloleucel (YESCARTA)	Diffuse large B-cell lymphoma (DLBCL), Primary mediastinal large B-cell lymphoma (PMBCL)	23/08/2018	✓ (CDF, MAA)[7]	× (EOL/ UO)[8]
Letermovir (PREVYMIS)	Cytomegalovirus infection following allogeneic haematopoietic stem cell transplant	08/01/2018	✓ (PAS)[9]	✓ (UO)[10]
Patisiran (ONPATTRO)	Hereditary transthyretin (hATTR) amyloidosis	27/08/2018	✓ HST (PAS)[11]	✓ (UO)[12]
Daunorubicin / cytarabine (VYXEOS)	Acute myeloid leukaemia (AML)	23/08/2018	✓ (PAS)[13]	✓ (EOL/ UO)[14]
Tisagenlecleucel (KYMRIAH)	B-cell acute lymphoblastic leukaemia (B-ALL) up to 25yrs	22/08/2018	✓ (CDF, MAA)[15]	✓ (EOL/ UO)[16]
Tisagenlecleucel (KYMRIAH)	Diffuse large B-cell lymphoma (DLBCL) relapsed/ refractory	22/08/2018	✓ (CDF, MAA)[17]	✓ (EOL/ UO)[18]
Ciclosporin (VERKAZIA)	Vernal keratoconjunctivitis (VKC), aged 4-18yrs	06/07/2018	-	✓(OM)[19]
Darvadstrocel (ALOFISEL)	Complex perianal fistulas in Crohn's disease	23/03/2018	× [20]	× (OM)[21]
Burosumab (CRYSVITA)	X-linked hypophosphataemia	19/02/2018	✓ HST (PAS)[22]	-

CDF, Cancer Drugs Fund; EMA, European Medicines Agency; EOL, end-of-life; MAA, Managed Access Agreement; OM, orphan medicine; PAS, Patient Access Scheme; UO, ultra-orphan; -, treatment not assessed.

A total of 21 orphan medicines were authorised by the EMA between 01/01/2018 and 01/09/2019 across 9 different disease areas. Ten were assessed by NICE and/ or SMC (**Table 2**). Of these:

- 6 were recommended by both NICE & SMC.
- 1 (ALOFISEL) was not recommended by NICE & SMC due to demonstrating a small clinical benefit with uncertain long-term benefit in a specific patient population, leading to uncertainties in cost-effectiveness estimates.
- 1 drug (CRYSVITA) was recommended by NICE (HST) but has not been assessed by SMC.
- 1 drug (VERKAZIA) was recommended by SMC but has not been assessed by NICE for the orphan indication.
- YESCARTA was recommended by NICE under the Cancer Drugs Fund for both DLBCL and PMBCL, but was not accepted by SMC following ultra-orphan assessment considering end-of-life criteria, due to insufficient justification of the cost of YESCARTA in relation to its treatment benefits, and an insufficiently robust economic analysis.
  - In the assessment of ultra-orphan medicines, the SMC can accept greater uncertainty in the economic case.
  - SMC stated that after considering YESCARTA within the context of the SMC decision modifiers applied in the case of high cost-effectiveness ratios[23], and the available evidence, the Committee could not accept YESCARTA for use within NHS Scotland.

Conclusions

- There are different NICE and SMC procedures for assessing treatments for orphan indications, leading to potential disparities in the availability of these treatments for NHS patients in England and Scotland e.g. YESCARTA.
- Both NICE and SMC do not consider rarity alone as sufficient reasoning to recommend medicines with high incremental cost-effectiveness ratios (ICERs).
- Although NICE has the HST process specifically for treatments for very rare diseases, policies exist within their STA process which can provide NHS patients with access to treatments for rare cancers, via Managed Access Agreement within the Cancer Drugs Fund.
- YESCARTA, PREVYMIS, VYXEOS, and KYMRIAH were considered for ultra-orphan evaluation by SMC, but not HST evaluation by NICE, highlighting a disparity between the criteria for evaluation under these specialised processes between the two HTA organisations.

References
1. EMA, 2007, Orphan drugs and rare diseases at a glance.
2. NICE, 2017, Interim Process and Methods of the Highly Specialised Technologies Programme: Updated to reflect 2017 changes.
3. Scottish Government, 2018, Treatments for rare conditions.
4. Scottish Government, 2019, A Guide to the Ultra-Orphan Pathway.
5. NICE, 2019, Inotersen for treating hereditary transthyretin amyloidosis [HST9]
6. SMC, 2019, Inotersen 284mg solution for injection in pre-filled syringe (Tegsedi®)
7. NICE, 2019, Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA559]
8. SMC, 2019, Axicabtagene ciloleucel 0.4 – 2 x 108 cells dispersion for infusion dispersion for infusion (Yescarta®)
9. NICE, 2019, Letermovir for preventing cytomegalovirus disease after a stem cell transplant [TA591]
10. SMC, 2019, Letermovir 240mg film-coated tablets (Prevymis®)
11. NICE, 2019, Patisiran for treating hereditary transthyretin amyloidosis [HST10]
12. SMC, 2019, Patisiran 2mg/mL concentrate for solution for infusion (Onpattro®)
13. NICE, 2018, Liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia [TA552]
14. SMC, 2019, Liposomal formulation of daunorubicin/cytarabine 44mg/100mg powder for concentrate for solution for infusion (Vyxeos®)
15. NICE, 2018, Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [TA554]
16. SMC, 2019, Tisagenlecleucel 1.2 x 106 – 6 x 108 cells dispersion for infusion (Kymriah®) Novartis Pharmaceuticals UK Ltd
17. NICE, 2019, Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]
18. SMC, 2019, Tisagenlecleucel 1.2 x 106 to 6 x 108 cells dispersion for infusion (Kymriah®)
19. SMC, 2018, Ciclosporin 1mg/mL (0.1%) eye drops emulsion (Verkazia®)
20. NICE, 2019, Darvadstrocel for treating complex perianal fistulas in Crohn's disease [TA556]
21. SMC, 2019, Darvadstrocel 30 million cells/6mL suspension for injection (Alofisel®)
22. NICE, 2018, Burosumab for treating X-linked hypophosphataemia in children and young people [HST8]
23. SMC, 2012, SMC modifiers used in appraising new medicines

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