National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pentosan polysulfate sodium for treating bladder pain syndrome

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	BAUS FNUU	There is no new evidence that I can find on that the most recent being the 2014 Nickel trial which showed no significant difference between this and placebo. There have however been several publication on the use of Botox for BPS	Comments noted. No changes to the scope are needed.
	Consilient Health	Consilient Health is of the opinion that Elmiron (pentosan polysulfate sodium) should not be referred to NICE for appraisal due to the small eligible patient population: there are only approximately 2 patients in 10,000 people (see reference below) with Bladder Pain Syndrome (BPS) showing endoscopically Hunner's lesions and/or glomerulations, representing the classical IC population (EAU / ESSIC classification 2C and 3C). Consequently the anticipated budgetary impact for the NHS is low. In April 2015, NICE published an evidence summary on pentosan polysulfate sodium (ESUOM 43), no additional clinical evidence has been generated. Additionally, in 2016/17 only 506 scrips have been written in primary care in the UK amounting to approximately 50 patients treated on the NHS. Data on the number of patients treated via secondary care are unavailable but	Comments noted. No changes to the scope are needed. Following the consultation exercise and the scoping workshop, NICE is of the opinion that an appraisal of pentosan polysulfate sodium for treating bladder pain syndrome is appropriate.

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		discussions with specialist importers suggest it is similar to primary care. Consequently Elmiron has had minimal impact on NHS resources. Going forward, patients eligible for treatment in England are approximately 9,000. Using the assumption that after 3 years, 30% of patients have received treatment* (2,700 patients) then the cumulative total of these scrips would be less than [redacted] spread over 3 years. In reality, these figures are likely to be far lower and closer to [redacted] over 3 years due to the limited use of cystoscopy with bladder distension to diagnose glomerulations and Hunner's lesions. In 2016/17 there were only 349 procedures (in-patient admissions**) for this indication undertaken (HES data, see Tables 1 and 2). Reference: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2017/07/human_orphan_001975.jsp&mid=WC0b01ac058001d12b * 30% is an ambitious target and in reality it is likely to be near 10% of patients treated. **Data for procedures undertaken as out-patients currently unavailable due to hospital administrative coding issues. However, even if exactly the same number of out-patient procedures were undertaken as for in-patient procedures it would only amount to 700 patients per year.	
Wording	BAUS FNUU	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* yes	Comment noted. No changes to the scope are needed.
	Consilient Health	Should the appraisal proceed, we believe that the remit would be better worded, in accordance with the restricted licensed indication, as follows: "To appraise the clinical and cost effectiveness of pentosan polysulfate sodium in the treatment of interstitial cystitis/bladder pain (IC/BPS) syndrome characterized by either glomerulations or Hunner's lesions (diagnosed by	Comments noted. The remit wording is to appraise pentosan polysulfate sodium within its marketing authorisation. This is defined in greater detail

<table>
<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
<tr><td></td><td></td><td>cystoscopy with hydrodistension) in adults with moderate to severe pain, urgency and frequency of micturition”.</td><td>elsewhere in the scope. No changes to the remit wording are needed.</td></tr>
<tr><td>Timing Issues</td><td>Consilient Health</td><td>Since the impact of the drug on NHS resources is so limited and there has been approximately 100 (primary care and secondary care) patients treated with Elmiron in the UK in 2016/17, there is limited urgency or need for this appraisal.</td><td>Comments noted.</td></tr>
<tr><td>Additional comments on the draft remit</td><td>Consilient Health</td><td>Table 1: In-patient patient cohorts with primary diagnosis code of chronic interstitial cystitis (N30.1) in NHS England in 2016/17: admission and cost details
<table>
<tr><th>Patient Cohort</th><th>Admission episodes</th><th>Patients</th><th>Patients per 100,000 population</th><th>Mean referral to treatment time in days</th></tr>
<tr><td>Interstitial cystitis / painful bladder syndrome patients coded with ICD-10 code N30.1</td><td>8,936</td><td>2,144</td><td>3.7</td><td>72.4</td></tr>
</table>
Table 2: Inpatient patient cohorts with primary diagnosis code of chronic interstitial cystitis (N30.1) in NHS England in 2016/17: admissions with operative procedures
<table>
<tr><th>Patient Cohort</th><th>Admissions with a bladder distension procedure</th><th>Admissions with a cystoscopy procedure</th><th>Admissions with urodynamic studies</th></tr>
</table></td><td>Information noted. No changes to the scope are needed.</td></tr>
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Section	Consultee/ Commentator	Comments [sic]						Action
		Interstitial cystitis / painful bladder syndrome patients coded with ICD-10 code N30.1	349*	512	0		60	7,527
		ICD-10 Code N30.1 "chronic interstitial cystitis" is not specific for the subgroup of patients with glomerulations or Hunner's lesions; patient numbers and admission numbers will include patients not eligible for elmiron. [1]patient count is provided in addition to admission count as the bladder instillation procedure tends to result in multiple admissions per patient per year ***Data for procedures undertaken as out-patients currently unavailable due to hospital administrative coding issues. However, even if exactly the same number of out-patient procedures were undertaken as for in-patient procedures it would only amount to 700 patients per year.**						

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Consilient Health	The second paragraph of this section could lead the reader to believe that the numbers of eligible patients for this treatment are between 15,000 and 150,000 based on epidemiological studies (Koziol JA, 1994). The estimation of the prevalence of "Bladder pain syndrome characterised by either glomerulations or Hunner's lesions" or "Interstitial Cystitis" is challenging due to the very variable terminology used for the condition. However, data available demonstrates a prevalence below the orphan threshold. A summary of epidemiological information for "Bladder pain syndrome characterised by either glomerulations or Hunner's lesions" in the EU based on a comprehensive research on the prevalence including scientific/medical databases (PubMed/Medline, SciSearch, Embase) is presented below.	Comments noted. The background section of the scope has been amended to include the EU prevalence estimate reported by the European Medicines Agency.

<table>
<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
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In a conservative approach the most recent figure from Austria of 0.9 per 10,000 is estimated to be the actual prevalence of “Bladder pain syndrome characterised by either glomerulations or Hunner’s lesions” in the EU. It is recognized that this figure has not been derived from a comprehensive epidemiological study but via a modelling approach based on survey data. However, even if it is assumed in a scenario analysis that the error of this approach is 100% the resulting prevalence would be 1.8 per 10,000, which is still well below the orphan threshold.

The data presented are supported by data from studies on the epidemiology of “Bladder pain syndrome characterised by either glomerulations or Hunner’s lesions” (or IC/BPS) in the US (Curhan et al. 1999, Clemens et al. 2005A, Roberts et al. 2003, Patel et al. 2008, Rosenberg et al. 2005, Payne et al. 2007, Berry et al. 2011).

This is recognised by the latest Orphan designations granted by the European Commission for pentosan polysulfate sodium for the treatment of interstitial cystitis (e.g. May 2016 to Nextrasearch di Gasparetto Adolfo & C., Sas, Italy (EU/3/16/1663) and January 2017 to Kyoto tech Limited, United Kingdom / HV-Polysaccharides GmbH & Co. KG, Germany, in June 2017 (EU/3/16/1822)).

Summary of prevalence information for IC/BPS in the EU
<table>
<tr><th>Country</th><th>Prevalence</th><th>Reference</th></tr>
<tr><td>Austria</td><td>0.9 per 10,000</td><td>Temml et al. 2007</td></tr>
<tr><td>Finland</td><td>1.1 – 6.7 or 10.2 per 10,000</td><td>Oravisto 1975,Leppilahti et al. 2002, 20</td></tr>
<tr><td>Netherlands</td><td>0.3 – 0.5 per 10,000</td><td>Bade et al. 1995</td></tr>
</table>

Therefore the eligible population for England is approximately 9,000.
The number of patients who will actually receive Elmiron is likely to be even smaller due to the requirement to have diagnosis confirmed by cystoscopy with hydrodistension. A procedure often requiring a hospital admission. In 2016/17 only 349 people who had the diagnosis ICD-10 code N30.1 (chronic
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</table>

Section	Consultee/ Commentator	Comments [sic]	Action
		interstitial cystitis/bladder pain syndrome) underwent this procedure (HES data – see tables above with data caveat). Reference: Koziol JA. Epidemiology of Interstitial Cystitis. Urol Clin North Am 1994;21:7-20. Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences. J Urol. 1995; 154(6): 2035-7. Berry, S. H., M. N. Elliott, M. Suttorp, L. M. Bogart, M. A. Stoto, P. Eggers, L. Nyberg, J. Q. Clemens (2011). "Prevalence of Symptoms of Bladder Pain Syndrome/Interstitial Cystitis Among Adult Females in the United States." J Urol. 186(2): 540–544. Clemens JQ, Meenan RT, Rosetti MC, Gao SY, Calhoun EA. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol 2005A; 173(1): 98-102. Clemens JQ, et al . Prevalence of interstitial cystitis symptoms in a managed care population. J Urol. 2005B; 174(2): 576-80. Curhan GC et al. Epidemiology of interstitial cystitis: a population based study. J Urol. 1999 Feb;161(2):549-52. Leppilahti M et al. Prevalence of symptoms related to interstitial cystitis in women: a population based study in Finland. J Urol. 2002; 168(1): 139-43. Leppilahti, M., J. Sairanen, T. L. Tammela, S. Aaltomaa, K. Lehtoranta, A. Auvinen and G. Finnish Interstitial Cystitis-Pelvic Pain Syndrome Study (2005). "Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland." J Urol 174(2): 581-583. Link, C. L., S. J. Pulliam, P. M. Hanno, S. A. Hall, P. W. Eggers, J. W. Kusek, J. B. McKinlay (2008). "Prevalence and Psychosocial Correlates of Symptoms Suggestive of Painful Bladder Syndrome: Results from the Boston Area Community Health (BACH) Survey." J Urol. 180(2): 599–606 Oravisto KJ. Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn. 1975; 64(2): 75-7. Patel R et.al. Incidence and clinical characteristics of interstitial cystitis in the community. Int Urogynecol J Pelvic Floor Dysfunct. 2008; 19(8): 1093-6. Payne, C.K., G. F. Joyce, M. Wise, J. Q. Clemens (2007). "Interstitial Cystitis and Painful Bladder Syndrome." J Urol 177:2042-9. Roberts RO et al. Incidence of physician-diagnosed interstitial cystitis in Olmsted County: a community-based study. BJU Int. 2003; 91(3): 181-5. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. J Urol. 2005; 174(6): 2231-4. Temml C et al. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol. 2007; 51(3): 803-8.	

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention	BAUS FNUU	I prefer the term bladder pain syndrome to interstitial cystitis	Comment noted. Following discussion at the scoping workshop it was agreed that 'bladder pain syndrome' is the most appropriate term for the condition. The title of the appraisal and the scope have been amended to reflect this.
	Consilient Health	Pentosan Polysulfate Sodium (PPS) is a heparin-like macromolecular carbohydrate derivative, which chemically and structurally resembles glycosaminoglycans i.e. it is not a "glycosaminoglycan". Relevant for the treatment of IC/BPS is the restoring effect of the GAG layer because of the structural similarity to glycosaminoglycans as well as the anti-inflammatory effect.	Comments noted. The technology section of the scope has been amended to accurately describe the technology.
Population	BAUS FNUU	*Is the population defined appropriately? Are there groups within this population that should be considered separately?* yes	Comment noted. No changes to the scope are needed.
	Consilient Health	The population needs to be clearly defined as "patients with IC/BPS with confirmed glomerulations and/or Hunner's lesions". There are no logical or valid reasons to consider Hunner's lesions or glomerulations separately.	Comments noted. The population is defined as "adults with bladder pain syndrome, characterised by either glomerulations or Hunner's lesions", as

Section	Consultee/ Commentator	Comments [sic]	Action
			per the marketing authorisation wording. The population will be considered as a whole. No changes to the scope are needed.
Comparators	BAUS FNUU	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?* yes	Comment noted. No changes to the scope are needed.
	Consilient Health	"Established clinical management" is very broad and could potentially include various unlicensed/off-label medicines or therapies including some interventions of limited proven value. Should this appraisal take place, we believe that it would be appropriate to limit the comparators in accordance with NICE guidance to licensed therapies. For the indication under consideration, we believe that this means that the only valid comparators are a group of medicinal devices known as bladder installations. Approved devices in the UK identified are as follows: Cystitstat (Hyaluronate sodium) – Teva Gepan (Chondroitin) – Purple Orchid Pharma Uracyst (Chondroitin) - Galen iAluRil (Hyaluronate sodium/chondroitin) - Aspire Hyacyst (Hyaluronate sodium) – Syner-Med Whilst these devices are approved for a broad range of urological indications, they are used in the IC/BPS patient group. They would appear from the in-	Comments noted. The comparator section has been amended to specify bladder instillations as the relevant comparator.

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		patient HES data to be a pre-dominant treatment for patients with a primary diagnosis of IC/BPS (ICD N30.1) with 7,527 admissions with bladder instillations being recorded in 2016/17 in 1,047 patients.	
Outcomes	BAUS FNUU	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* yes	Comment noted. No changes to the scope are needed.
	Consilient Health	GRA, pain, urgency A primary meta-analysis has been conducted which evaluated the effect of PPS on patient reported global assessment (GRA) improvement. As it is well known that specific symptoms of the disease are perceived more burdensome than others, e.g. pain might be the most burdensome symptom for one patient, while for the other frequency is far more burdensome than pain. This perception of burden associated with the single symptoms is very subjective and differs from patient to patient. Accordingly, if the patients assess their "global response" the GRA is the best integral tool to measure the impact of therapy on the patient's individual and subjective burden of disease.	Comments noted. The means of measuring the outcomes set out in the scope are not specified, in order to keep the scope broad and not unnecessarily exclude different types of measures. No changes to the scope are needed.
Economic analysis	Consilient Health	We would appreciate a commercial in confidence discussion around the appropriate time horizon for the analysis and generation of utility values.	Comments noted. No changes to the scope are needed.
Equality and Diversity	Consilient Health	None	Comment noted. No action required.
Other considerations	BAUS FNUU	amitryptalline is well established as a treatment. IIntravesical botulinum toxin is being evaluated for this indication	Comments noted. Following discussion at the scoping workshop it was noted that

Section	Consultee/ Commentator	Comments [sic]	Action
			medicines to treat the symptoms of the condition, such as amitriptyline are likely to be given alongside the technology under consideration. It was also agreed that bladder instillations are the relevant comparator. The comparators section of the scope has been amended to reflect this.
	Consilient Health	None	Noted.
Innovation	BAUS FNUU	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* no	Comment noted.
	Consilient Health	Elmiron (pentosan polysulfate sodium) was approved by the EMA in June 2017 as a new chemical entity and is the first and only licensed medicine for the treatment of people with interstitial cystitis/bladder pain syndrome with glomerulations or Hunner's lesions. All other treatments currently approved in the UK for this indication are devices. These treatments are invasive, typically requiring a hospital admission or outpatient appointment. Patients who are started on these	Comments noted. No changes to the scope are needed.

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		treatments usually require weekly bladder instillations for the first 4 to 6 weeks and then monthly thereafter. Elmiron, is a step change in the management of this condition. Whilst it should be initiated in a secondary care environment following specialist diagnosis, it is an oral therapy and does not require an admission to hospital. Following initiation, treatment can be continued in the community. We have not currently identified any potential significant health related-benefits that are unlikely to be included in QALY calculations. That said, a Commercial in Confidence meeting with NICE is requested post the open Scoping Workshop	
Questions for consultation	Consilient Health	*Which treatments are considered to be established clinical practice in the NHS for interstitial cystitis?* The question is too broad as there is no established clinical practice, therefore the remit should be only IC/BPS patients with glomerulations or Hunner's lesions diagnosed by cystoscopy. For this defined indication, the only other treatments that are approved in the UK are a group of medicinal devices called bladder installations (they have a broad indication in urology which includes IC/BPS with glomerulations and Hunner's lesions). Identified named brands and manufacturers available in the UK are noted above. *Would pentosan polysulfate sodium be used in addition to established clinical practice?* Following diagnosis of IC/BPS with glomerulations or Hunner's lesions with cystoscopy, a treatment choice could be made between Elmiron and a bladder installation device (see above). Either treatment pathway could be accompanied by some of recommendations made by NHS Choices eg. Dietary advice, analgesia depending on individual patient needs.	Comments noted. The comparator section of the scope has been amended to specify bladder instillations as the relevant comparator. No other changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant comparators for pentosan polysulfate sodium been included in the scope? No. See earlier comments on Comparators. *Where do you consider pentosan polysulfate sodium will fit into the existing NICE pathway?* Urological Conditions *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* Given that the indication for Elmiron is for patients with IC/BPS characterised by glomerulations or Hunner's lesions and that the only means of definitely diagnosing the presence of these lesions is through cystoscopy with hydrodistension, which implies anaesthesia of the patient, then the limited use of this diagnostic tool in England is a potential barrier to uptake.	
Additional comments on the draft scope	BAUS FNUU	There is little good evidence that this treatment is effective	Comment noted. No changes to the scope are needed.
	Consilient Health	None	Noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health and Social Care
United Kingdom Clinical Pharmacy Association (Women's Health Group)