APPENDIX

Supplementary Table 1. PICO format for priority questions	
1. Is oral pentosan polysulfate (Elmiron) indicated for the treatment of IC/BPS?	**P** Patients with IC/BPS **I** Oral PPS **C** Standard of care (conservative measures) or placebo **O** 1. Reduction in ICSI/ICPI scores 2. Reduction in pain 3. Adverse events 4. Medication-induced maculopathy
2. What is the optimal intravesical cocktail for the treatment of IC/BPS	**P** IC/BPS patients **I** 1. Multi-drug cocktail 2. Lidocaine 3. Heparin 4. Chondroitin sulfate 5. Haluronic acid 6. Other (*most recent CUA guideline: RTX and BCG NOT recommended therefore not included in this review) **C** DMSO or placebo **O** 1. Reduction in ICSI/ICPI scores 2. Reduction in pain 3. Adverse events 4. Urinary tract infection
3. Is intradetrusor onabotulinumtoxin-A indicated for the treatment of IC/BPS?	**P** IC/BPS patients who have failed at least one other treatment **I** Intradetrusor onabotulinumtoxinA ± hydrodistension **C** Placebo or hydrodistension **O** 1. Reduction in ICSI/ICPI scores 2. Reduction in pain 3. Adverse events 4. Acute urinary retention/need to initiate CIC 5. Urinary tract infection
4. What is the optimal treatment modality for treating Hunner lesion-IC/BPS?	**P** Hunner lesion-IC/BPS patients **I** 1. Resection of Hunner lesion 2. Laser ablation for Hunner lesion 3. Steroid injection into Hunner lesion

	C Direct cauterization/fulguration of Hunner lesion **O** 1. Improvement in ICSI/ICPI scores 2. Time to recurrence of Hunner lesions 3. Time to retreatment of Hunner lesions 4. Improvement in pain 5. Adverse events
5. Is oral cyclosporin A indicated for the treatment of IC/BPS?	**P** Patients with IC with or without Hunner lesions who have failed two prior treatments **I** Cyclosporin A **C** 1. Conservative treatment 2. Oral pentosan polysulfate sodium **O** 1. Efficacy: Subjective (i.e. Interstitial Cystitis Symptom Index (ICSI) or Interstitial Cystitis Problem Index scores) and Objective (i.e., change in bladder capacity) 2. Adverse events: Systemic (i.e., renal deterioration and hypertension) and local (scarring, urinary tract infection, bleeding). Other outcomes may include tolerability, resistance and compliance.

Supplementary Tables 2A and 2B. Summary of findings: Is pentosan polysulfate (Elmiron) indicated for the treatment of IC/BPS?
A.

Summary of findings:

Oral PPS compared to standard of care or placebo for IC/BPS

Patient or population: IC/BPS
Setting: Urology clinics
Intervention: Oral PPS
Comparison: Standard of care or placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care or placebo	**Risk with oral PPS**				
Proportion of participants whose symptoms were cured or improved (symptom cured/improved) assessed with pairwise meta-analysis followup: median 3 months	309 per 1000	**374 per 1000** (270–490)	**OR 1.34** (0.83–2.15)	387 (3 RCTs)	⊕⊕◯◯ Low[a,b]	Compared to the NMA, we only included studies that addressed oral PPS. In every 1000 patients who receive PPS compared to placebo, 65 more participants (95% CI from 39 fewer to 181 more) experience symptom improvement. The definition of symptom improvement varied among the included trials.
Pain assessed with pairwise meta-analysis followup: range 12 weeks to 24 weeks	The mean pain ranged from **-1.5 to -0.4** on 0–10 scale	MD **0.1 on 0–10 scale lower** (0.58 lower to 0.36 higher)	–	387 (3 RCTs)	⊕◯◯◯ Very low[a,b,c]	We assumed the SD from Nickel 2015 for the study that did not report SD and for recalculating the pooled SMD to MD. included studies have wide CIs with point estimates indicating benefit, no effect, and harm for PPS.

Summary of findings:

Oral PPS compared to standard of care or placebo for IC/BPS

Patient or population: IC/BPS
Setting: Urology clinics
Intervention: Oral PPS
Comparison: Standard of care or placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care or placebo	**Risk with oral PPS**				
ICSI assessed with: Single study direct comparison followup: mean 6 months	The mean ICSI was **-2.3** units change from baseline	MD **0.6 units change from baseline higher** (1.21 lower to 2.41 higher)	–	49 (1 RCT)	⊕◯◯◯ Very low[d,e]	Only the trial by Sant 2003 reports on the ICSI and ICPI score change from baseline in the oral PPS and placebo groups. The study by Nickel 2015 used ICSI to ascertain responders but did not report on scores in the trial arms. The ICSI score ranges from 0–20 with higher scores representing worse symptoms. A mean score of 0.6 represents a 0.03% change on the whole scale.
ICPI assessed with: Single study direct comparison followup: mean 6 months	The mean ICPI was **-2.3** units change from baseline	MD **0.4 units change from baseline higher** (1.39 lower to 2.19 higher)	–	49 (1 RCT)	⊕◯◯◯ Very low[d,e]	Only the trial by Sant 2003 reports on the ICSI and ICPI score change from baseline in the oral PPS and placebo groups. The study by Nickel 2015 used ICSI to ascertain responders but did not report on scores in the trial arms. The ICPI score ranges from 0–16, with higher scores representing the worse quality of life. A mean score of 0.4 represents a 0.04% change on the whole scale.

Summary of findings:

Oral PPS compared to standard of care or placebo for IC/BPS

Patient or population: IC/BPS
Setting: Urology clinics
Intervention: Oral PPS
Comparison: Standard of care or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care or placebo	**Risk with oral PPS**				
Any maculopathy assessed, including atypical maculopathy and AMD followup: mean 5 years	26 per 1000	**28 per 1,000** (24 to 31)	**OR 1.06** (0.93–1.21)	61995 (2 non-randomized studies)	⨁⨁◯◯ Low[f]	The current literature around PPS-associated maculopathy uses different methodologic designs and cannot be only summarized in poolable administrative cohort studies. This condition has been described as unique retinal changes distinct from other pathologies. The prevalence of this maculopathy is believed to be associated with long-term and high cumulative dose exposure to PPS. Considering these, the interpretation of the certainty from only cohort studies should be with caution.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; OR: odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

Doiron et al. 2025 Canadian Urological Association Guideline: Selected treatment recommendations for interstitial cystitis/bladder pain syndrome

[a]Rated down by 1 level for the risk of bias. None of the studies are at low risk of bias due to attrition. The point estimates are somehow different in studies at lowest risk of bias
[b]Rated down for imprecision by 1 level. The confidence interval crosses the line of no effect, and the total number of included participants is limited. The boundaries of the CI warrant different interpretations of the results.
[c]Rated down by 1 level for inconsistency. The visual inspection of the forest plot reveals that the effect estimates from different studies point in opposite direction and convey different messages.
[d]Rated down by 1 level for risk of bias. The only included study is at a high risk of bias for attrition and unclear risk of bias for selection, performance, and detection bias.
[e]Rated down by 2 levels for imprecision due to the width of the CI and the very few numbers of included participants.
[f]Rated down by one level for risk of bias. The studies in the analysis use a retrospective cohort design based on administrative data with a high risk of outcome ascertainment and possibly insufficient follow-up time. We also decided to rate up the certainty to acknowledge some additional information from studies and design beyond the included studies in the meta-analysis. According to the current literature, studies suggest that PPS-associated maculopathy can happen after long exposure (years) to PPS at high cumulative doses. This entity has unique presentations that are different from other maculopathies. Dose-response relationships have also been observed.

B.

Summary of findings:

Oral PPS compared to standard of care or placebo for IC/BPS

Patient or population: IC/BPS
Setting: Urology clinics
Intervention: Oral PPS
Comparison: Standard of care or placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care or placebo	**Risk with oral PPS**				
Proportion of participants whose symptoms were cured or improved (Symptom cured/improved) assessed with: NMA followup: median 3 months	262 per 1,000	**288 per 1,000** (124 to 543)	**OR 1.14** (0.40 to 3.35)	1000 (6 RCTs)	⨁◯◯◯ Very low[a]	The majority of trials were small (only 5 reporting with >100 patients). The majority of pairwise comparisons in the network had considerable heterogeneity, but the results of closed loops direct and indirect comparisons were mostly consistent. Further explanation on GRADE judgments is not available. The results suggest that 26 more patients (95% CI from 138 fewer to 281 more) would experience symptom improvement out of every 1000 IC/BPS patients who receive PPS compared to control.

Summary of findings:

Oral PPS compared to standard of care or placebo for IC/BPS

Patient or population: IC/BPS
Setting: Urology clinics
Intervention: Oral PPS
Comparison: Standard of care or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care or placebo	**Risk with oral PPS**				
Pain assessed with: NMA followup: median 3 months	The mean pain ranged from **2.6–9.4**	MD **0.42 higher** (1.04 lower to 1.91 higher)	–	(4 RCTs)	⊕◯◯◯ Very low[b]	The majority of trials were small. The majority of pairwise comparisons in the network had considerable heterogeneity, but the results of closed loops direct and indirect comparisons were mostly consistent. Given the size of the trials, the confidence intervals were wide. Further explanation on GRADE judgments is not available. The NMA authors considered a minimally important difference of 2.5 units.
ICSI assessed with: NMA followup: median 3 months	The mean ICSI was **0**	MD **1.18 higher** (1.1 lower to 3.45 higher)	–	(5 RCTs)	–	There is no further information provided by the authors of the NMA.
ICPI assessed with: NMA followup: median 3 months	The mean ICPI was **0**	MD **2.66 higher** (0.16 lower to 5.59 higher)	–	(2 RCTs)	–	There is no further information provided by the authors of the NMA.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; OR: odds ratio

Doiron et al. 2025 Canadian Urological Association Guideline: Selected treatment recommendations for interstitial cystitis/bladder pain syndrome

Summary of findings:

Oral PPS compared to standard of care or placebo for IC/BPS

Patient or population: IC/BPS
Setting: Urology clinics
Intervention: Oral PPS
Comparison: Standard of care or placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care or placebo	**Risk with oral PPS**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]Rated down for Risk of bias and imprecision. Further explanation is unavailable.
[b]Rated down for risk of bias and inconsistency. Further explanation is unavailable.

Supplementary Table 3. Summary of findings: Is intradetrusor Botox indicated for the treatment of IC/BPS?

Summary of findings:

Intradetrusor Botox compared to Control for IC/BPS

Patient or population: IC/BPS
Setting:
Intervention: Intradetrusor Botox
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	**Risk with intradetrusor Botox**				
Pain assessed with: VAS (0–10 scale) followup: range 30–90 days	The mean pain was **4.9**	MD **0.57 lower** (1.33 lower to 0.2 higher)	–	213 (4 RCTs)	⨁⨁◯◯ Low[a,b]	Intradetrusor Botox may result in little to no difference in pain.
UTI followup: range 30–90 days	123 per 1000	**165 per ,000** (74–372)	**RR 1.34** (0.60–3.02)	166 (4 RCTs)	⨁◯◯◯ Very low[c,d,e]	The evidence is very uncertain about the effect of intradetrusor Botox on UTI.
Acute urinary retention followup: range 30–90 days	69 per 1000	**108 per 1000** (30–381)	**RR 1.56** (0.44–5.53)	154 (3 RCTs)	⨁◯◯◯ Very low[e,f]	The evidence is very uncertain about the effect of intradetrusor Botox on acute urinary retention.
ICSI scale from: 0–19 followup: range 30–90 days	The mean ICSI was **10.86**	MD **1.64 lower** (3.01 lower to 0.26 lower)	–	200 (4 RCTs)	⨁◯◯◯ Very low[g,h,i]	The evidence is very uncertain about the effect of intradetrusor Botox on ICSI.
ICPI scale from: 0–16 followup: range 30–90 days	The mean ICPI was **10.08**	MD **1.71 lower** (3.01 lower to 0.42 lower)	–	200 (4 RCTs)	⨁◯◯◯ Very low[g,h,i]	The evidence is very uncertain about the effect of intradetrusor Botox on ICPI.

Doiron et al. 2025 Canadian Urological Association Guideline: Selected treatment recommendations for interstitial cystitis/bladder pain syndrome

Summary of findings:

Intradetrusor Botox compared to Control for IC/BPS

Patient or population: IC/BPS
Setting:
Intervention: Intradetrusor Botox
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	**Risk with intradetrusor Botox**				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a]Only one study is at low risk of bias with a 30% weight of the analysis.
[b]There is a quite wide CI with a very low total number of participants.
[c]Only one study is at low risk of bias with a 13% weight of the analysis.
[d]The effect estimates cover a very wide range with quite different implications.
[e]The number of events is extremely low leading to very wide CI.
[f]There is only one study at low risk of bias with only 16% weight of the analysis.
[g]More than 50% of the analysis weight comes from studies at a high risk of bias. Studies at low risk of bias have discrepancies in the effect estimates and have a limited sample size.
[h]One study at low risk of bias has a considerably different effect estimate from the rest of the studies. The implications of this different effect estimate are different from the others.
[i]The total number of participants in the analysis is limited.

Supplementary Table 4. Summary of findings: What is the optimal treatment modality for treating Hunner lesion-IC/BPS?

Summary of findings:

Treatment compared to no treatment for Hunner lesion-type IC

Patient or population: Hunner's lesion type IC
Setting:
Intervention: Treatment
Comparison: No treatment

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	**Risk with treatment**				
Pain (triamcinolone injection) assessed with: VAS scale from: 0–10	The mean pain (triamcinolone injection) was **2.95**	MD **2.8 lower** (6.13 lower to 0.53 higher)	–	372 (2 observational studies)	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of this treatment on pain.
ICPI (oral steroid)	The mean ICPI (oral steroid) was **12.2**	MD **2.19 lower** (4.68 lower to 0.3 higher)	–	28 (1 observational study)	⊕◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on ICPI.
ICSI (oral steroid)	The mean ICSI (oral steroid) was **14.7**	MD **3.8 lower** (7.02 lower to 0.58 lower)	–	28 (1 observational study)	⊕◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on ICSI.
Pain (Fulguration) assessed with: VAS scale from: 0–10	The mean pain (fulguration) was **7.7**	MD **5.65 lower** (6.75 lower to 4.56 lower)	–	182 (3 observational studies)	⊕◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on pain.
ICPI (fulguration)	The mean ICPI (fulguration) was **13.8**	MD **9.6 lower** (12.18 lower to 7.02 higher)	–	54 (1 observational study)	⊕◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on ICPI.

Summary of findings:

Treatment compared to no treatment for Hunner lesion-type IC

Patient or population: Hunner's lesion type IC
Setting:
Intervention: Treatment
Comparison: No treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	**Risk with treatment**				
ICSI (fulguration)	The mean ICSI (fulguration) was **15.1**	MD **7.9 lower** (10.74 lower to 5.06 lower)	–	54 (1 observational study)	⨁◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on ICSI.
Pain (TUR) assessed with: VAS scale from: 0–10	The mean pain (TUR) was **9.18**	MD **7.83 lower** (7.93 lower to 7.73 lower)	–	218 (2 observational studies)	⨁◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on pain.
Pain (TUR + HD) assessed with: VAS scale from: 0–10	The mean pain (TUR + HD) was **9.7**	MD **8.4 lower** (8.52 lower to 8.28 higher)	–	44 (1 observational study)	⨁◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on pain.
Pain (major reconstructive surgery) assessed with: VAS scale from: 0–10	The mean pain (major reconstructive surgery) was **8.3**	MD **7 lower** (7.9 lower to 6.1 higher)	–	80 (1 observational study)	⨁◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on pain.
ICPI (major reconstructive surgery)	The mean ICPI (major reconstructive surgery) was **14.6**	MD **8.1 lower** (9.56 lower to 6.64 lower)	–	80 (1 observational study)	⨁◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on ICPI.

Summary of findings:

Treatment compared to no treatment for Hunner lesion-type IC

Patient or population: Hunner's lesion type IC
Setting:
Intervention: Treatment
Comparison: No treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	**Risk with treatment**				
ICSI (major reconstructive surgery)	The mean ICSI (major reconstructive surgery) was **17.8**	MD **7.9 lower** (9.73 lower to 6.07 lower)	–	80 (1 observational study)	⊕◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on ICSI.
Pain (Botox injection) assessed with: VAS scale from: 0–10	The mean pain (Botox injection) was **6.3**	MD **3.4 lower** (4.43 lower to 2.37 lower)	–	20 (1 observational study)	⊕◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on pain.
ICPI (Botox)	The mean ICPI (Botox) was **1.8**	MD **5.9 lower** (6.87 lower to 4.93 lower)	–	20 (1 observational study)	⊕◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on ICPI.
ICSI (Botox)	The mean ICSI (Botox) was **16.6**	MD **6.6 lower** (8.21 lower to 4.99 lower)	–	20 (1 observational study)	⊕◯◯◯ Very low[a]	The evidence is very uncertain about the effect of this treatment on ICSI.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference

Doiron et al. 2025 Canadian Urological Association Guideline: Selected treatment recommendations for interstitial cystitis/bladder pain syndrome

Summary of findings:

Treatment compared to no treatment for Hunner lesion-type IC

Patient or population: Hunner's lesion type IC
Setting:
Intervention: Treatment
Comparison: No treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	**Risk with treatment**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a]Observational studies without a control group (before-after design) are at a very serious risk of bias.
[b]No overlap in the ES from included studies.