EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2016
EMA/287422/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

elmiron

International non-proprietary name: pentosan polysulfate sodium

Procedure No. EMEA/H/C/004246/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE Adverse event

API active pharmaceutical ingredient

aPTT activated partial thromboplastin time

ASMF Active Substance Master File

ATUn Autorisation Temporaire d'Utilisation nominative

AUA American urology association

BC maximal bladder capacity

BCS Biopharmaceutics Classification System

BPS bladder pain syndrome

CEP Certificate of Suitability of the EP

CFU Colony forming units

CI 95 % confidence interval

DDD defined daily doses

DDI Drug drug interaction

DMSO Dimethyl sulfoxide

EAU European Association of Urology

EC European Commission

ESSIC International Society for the Study of Bladder Pain Syndrome

EU European Union

FDA Food and Drug Administration

FT-IR Fourrier Transform Infrared Spectroscopy

GAG Glycosaminoglycan

GPC Gel permeation chromatography

GRA global response assessment

GTI gastrointestinal

HDPE High Density Polyethylene

HPLC high performance liquid chromatography

HSCIC Health and Social Care Information Centre

IC Interstitial Cystitis

ICH International Conference on Harmonisation of Technical Requirements for Registration of

ICPI O'Leary-Sant Interstitial Cystitis Problem Index

ICSI O'Leary-Sant Interstitial Cystitis Symptom Index

lgG Immunoglobulin G

INR International Normalized Ratio

IRA investigator RA

IR Infrared

ITT Intention to Treat

IV, i.v. Intravenous

LIVIVO German National Library of Medicine

LOCF last-observation-carried forward

LoD loss of drying

MAA Marketing Authorisation Application/Marketing Authorisation Applicant

MCC Microcrystalline Cellulose

MO Major Objection

MOA Mechanism of action

MTD Maximum Tolerated Dose

N/A not applicable/ available

NIDDK National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (USA)

NLT not less than

NMR Nuclear Magnetic Resonance

NMT not more than

NS not significant

OC Other Concern

PBS Painful Bladder Syndrome

Pbo Placebo

PD pharmacodynamics

Ph. Eur. European Pharmacopoeia

PI Prescribing Information

PK Pharmacokinetic

P.O Per Os

PORIS Patient's overall rating of Symptoms Index

PP Polypropylene

PRA Patient responder analyis

PRO patient reported outcome

PPS Pentosan Polysulfate Sodium

PT Prothrombin time

PTT Partial Thromboplastin Time

PVC Polivinyl chloride

QD Once daily

QOL Quality of Life

Q&A Questions and Answers

RA Responder analysis (Assessment)

RH Relative Humidity

RIA Radioimmunoassay

RP HPLC reverse phase high performance liquid chromatography

Rx treatment arm

SAE Serious adverse event

SEC Size-exclusion chromatography

SmPC Summary of Product Characteristics

TCA trichloroacetic acid

TID, t.i.d. Three times daily

TLC Thin layer chromatography

Tmax Time of Maximum concentration observed

TSE Transmissible Spongiform Encephalopathy

TUR Transurethral resection

UV Ultraviolet

XRD X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant bene-Arzneimittel GmbH submitted on 4 February 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for elmiron, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 June 2015.

elmiron was designated as an orphan medicinal product EU/3/14/1411 on 15 January 2015 in the following condition: 'Treatment of Interstitial Cystitis'.

Following the CHMP positive opinion and at the time of the review of the orphan designation by the Committee on Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 11.04.2017 on request of the sponsor.

The applicant initially applied for the following indication:

'elmiron is indicated in adults for the treatment of Interstitial Cystitis'. During the procedure, on 01.03.2017, the applied indication was changed to 'elmiron is indicated for the treatment of bladder pain syndrome characterized by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition'.

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol Assistance

The applicant received protocol Assistance from the CHMP on 23 July 2015. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich Co-Rapporteur: Romaldas Mačiulaitis

- The application was received by the EMA on 4 February 2016.
- The procedure started on 25 February 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 May 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 May 2016.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 May 2016.
- During the meeting on 23 June 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 June 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 6 September 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 October 2016.
- During the PRAC meeting on 27 October 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 28 October 2016.
- During the CHMP meeting on 10 November 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 January 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 February 2017.
- During a meeting of an ad hoc Expert group on 30 January 2017, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 20 February 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 23 March 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to elmiron.

2. Scientific discussion

2.1. Problem statement

Oral pentosan polysulfate sodium (PPS) is already approved under the invented name Elmiron in Canada for the initial and maintenance treatment of interstitial cystitis (IC) since April 1993, in Australia for the treatment of IC since February 1994 and in the United States for relief of bladder pain or discomfort associated with IC since September 1996. Regulatory approval of the product in Canada, Australia and in the United States was mainly based on the favourable results of two pivotal clinical trials showing subjective improvements in pain, urgency, frequency and nocturia under treatment with PPS compared to placebo (Mulholland et al 1990, Parsons et al 1993).

The term BPS (bladder pain syndrome) rather than interstitial cystitis (IC) was put forward by the International Society for the Study of BPS (ESSIC) and is currently used in European guidelines and by the experts in the field. In accordance with the advice of the ad hoc expert group convened during this procedure and the ESSIC classification (Engeler et al 2015) the CHMP considered that the definition of former IC at the time when most of the pivotal studies were performed would, as per todays classification, fall under BPS characterized by glomerulations or Hunner's lesions (i.e. BPS type 2X – 3C.

2.1.1. Disease or condition

Interstitital Cystitis (IC) is a chronic, debilitating disorder, distressing bladder condition, which is characterised by pelvic pain associated with bladder filling, pollakiuria with a voiding frequency of more than eight urinations per day and more than two urinations per night, cystoscopic lesions (petechiae, Hunner's ulcers) revealed by a bladder hydrodistention test, and/or histological anomalies such as inflammatory mononuclear cell infiltrates and tissue granulation, in the absence of infection or any other pathology. The clinical picture is dominated by pain and pollakiuria. Although the pain is usually described as pelvic, it may also involve the perineum, vagina, suprapubically radiating to the groins, rectum, sacrum, scrotum and urethra. It becomes more severe upon bladder filling with relief after urination. The pollakiuria is the consequence of a nearly constant urge to urinate, which increases with bladder filling and is relieved by urination. However, patients do not display urinary incontinence and have symptoms of interstitial cystitis for an average of 7 years before diagnosis is made.

2.1.2. Epidemiology

Interstitial cystitis is a rare condition. 90% of the patients are afflicted women in their fifth and sixth decades of life. Symptoms often resemble those of patients with overactive bladder. Up to 50% of patients with symptoms of interstitial cystitis will have spontaneous resolution in time.

2.1.3. Aetiology and pathogenesis

There are many and different hypotheses about the causes of IC, including infection, inflammation, autoimmune mechanisms, hormonal troubles, defects in the urothelial glycosaminoglycan layer, hypoxia, and central neurologic mechanisms.

The aetiology is unknown but some triggering factors such as certain acid foods (coffee or citrus products), bacterial cystitis, pelvic surgery, delivery are hypothesised.

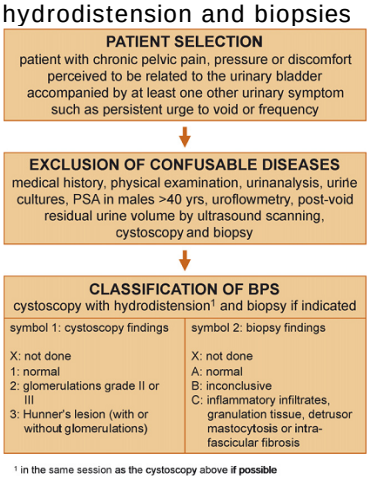
Other pathologies can be associated such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma and systemic lupus erythematosus.

2.1.4. Clinical presentation, diagnosis

The diagnosis of IC / BPS is primarily one of exclusion, using symptoms, examination, urine analysis and urine culture (to rule out a urinary tract infection), cystoscopy with hydrodistension (to rule out bladder cancer, vesical stones, urethral diverticula and intravesical foreign bodies), and biopsy (to exclude other pathologies).

Differentiation is reflected in the standardised scheme for the classification of BPS Types as published by the European Society for the Study of IC/PBS (ESSIC) (see Table 1). Cases meeting the ESSIC classification 2X to 3C would meet the NIDDK criteria for IC.

Table 1 ESSIC classification of types of BPS according to the results of cystoscopy with hydrodistension and biopsies



	Cystoscopy with hydrodistention			
	Not done	Normal	Glomerulations[a]	Hunner's lesion[b]
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive[c]	XC	1C	2C	3C

[a] Cystoscopy: glomerulations grade 2–3.
[b] With or without glomerulations.
[c] Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

2.1.5. Management

There is no consensus regarding the optimal treatment approach for this condition. The difficulty in treating IC/BPS derives from several factors, including (i) the lack of a clear understanding of the aetiology of the disorder. This precludes development of therapies targeted at the underlying pathophysiology; (ii) the symptoms of IC/BPS vary considerably across patients; (iii) the definitions of the condition and of measure of therapeutic outcomes vary; (iv) there are few high quality data (e.g., randomized trials) regarding the efficacy and safety of IC/BPS treatments. No treatment is consistently effective in providing relief for all patients.

All available treatment options thus far are purely symptomatic. There are no medicinal products approved for the treatment of IC in Europe. Current treatment options include:

- Off-label enteral and parenteral use of medicinal products (analgesics, corticosteroids, anti-allergics, PPS, Hydroxyzine, Amitriptyline, antibiotics, immunosuppressants, Gabapentin, Pregabalin, and Quercetin)

- Bladder (hydro-) distension
- Intravesical application of medicinal products and medical devices (DMSO, PPS…)
- Surgery

Existing evidence of efficacy and safety of PPS, when used for relief of bladder pain and other signs and symptoms of IC, lead to the recommendation to use PPS in European Treatment Guidelines for the treatment of bladder pain syndrome or IC. In the Guidelines on Chronic Pelvic Pain, which are released by the European Association of Urology since 2004 (Fall et al. 2004) oral usage of PPS is recommended as standard treatment for the therapy of bladder pain syndrome "BPS" already in the first version of these guidelines from 2004 until 2015 (strong recommendation (A) was given with a grade 1a level of evidence). In addition, a review article on treatment guidelines for classic and non-ulcer IC from the year 2000 lists oral treatment with PPS as an established treatment option for IC (Peeker et al. 2000). However, the guideline of the American Association of Urology published in 2014, gives a more conservative recommendation (evidence level given as "B") due to conflicting results of clinical studies and the guideline of the 5th International consultation on incontinence (Paul Abrams et al, 5th edition 2013) gives a grade recommendation of D with a level of evidence 1.

In the respective US treatment guideline (AUA guideline, 2014), PPS is recommended as second-line treatment (Grade B recommendation) after patient education, self-care practices and behavioural modifications or stress management practices, which are recommended as first-line treatment for IC in the US (Hanno et al.,2014).

Indeed, there are many therapeutic approaches for IC/BPS and none are proven to be helpful for all patients with IC/BPS. One of the **standards of care** is to treat IC/BPS with a **stepwise approach** (therapies for IC/BPS vary by the risk of adverse effects and the invasiveness of the treatment). **1st line**: self-care and behaviour modification (local heat or cold over the bladder or perineum, avoidance of activities or food or beverages that exacerbate symptoms, fluid management, Bladder training with urge suppression); **2nd line:** physical therapy (treatment of the pelvic muscle tender points, trigger points, connective tissue restrictions, and muscular abnormalities of the soft tissues by a physical therapist) and oral medications (amitriptyline, pentosan polysulfate sodium (**PPS**), antihistamines (eg, hydroxyzine); **3rd line:** bladder hydrodistention, treatment of Hunner lesions (by resection, electrical cauterization, or injection of these lesions with a corticosteroid), and intravesical dimethyl sulfoxide; **4th line**: intradetrusor botulinum toxin and sacral neuromodulation; 5th line: Cyclosporine A; 6th line: urinary diversion (removing the ureters from the bladder and diverting the urine into an incontinent urostomy or a continent catheterizable urine pouch). An **alternative approach** is an individualized treatment plan tailored to the patient's primary symptoms.

The most recent version of the European Guidelines on Chronic Pelvic Pain (Engeler et al., 2015) recommend to always consider multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments. For patients with BPS Type 3C, who have Hunner's lesions at cystoscopy, treatment with Transurethral resection (TUR) or laser was recommended if the patient is eligible. In case the patient is not eligible or the response is inadequate for these interventional treatments initiation of treatment with oral agents is recommended.

About the product

The active substance pentosan polysulfate sodium (PPS) is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative, which chemically and structurally resembles glycosaminoglycans.

PPS is a low molecular weight heparin-like compound. It has anticoagulant, fibrinolytic, and anti-inflammatory effects. The exact mechanism of action of PPS in the treatment of IC/BPS is unknown. It is hypothesized, that a potential barrier function of PPS instead of the damaged urothelial mucus might play a role as well the anti-inflammatory activity of PPS.

Indication

elmiron is indicated for the treatment of bladder pain syndrome characterized by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition

Posology

The recommended dose of pentosan polysulfate sodium is 300 mg/day taken as one 100 mg capsule orally three times daily.

Type of Application and aspects on development

elmiron is submitted under Article 10a (well-established use) of Directive 2001/83/EC (as amended) via the centralised procedure.

In accordance with Article 10a of Directive 2001/83/EC the application shall rely on appropriate scientific literature substituting non-clinical tests and clinical studies if it can be demonstrated that the active substance of a medicinal product has been in well-established medicinal use within the European Union for at least 10 years**,** with a recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply.

The requirements, described in Article 10a read in combination with the abovementioned Annex I, are discussed below:

(1) The time over which PPS has been used in Europe for the treatment of IC:

The first information on the usage of PPS in European Union is provided in publications of clinical studies conducted in the EU for the treatment of IC in 1986 – 1997 : an early case report about the use of PPS in 11 patients with IC was published in Germany (Beer et al 1986) , a multicentre open-label study in 87 patients conducted in 12 centres in Sweden and 5 centres in Finland (Fritjfsson et al 1987), including one of the pivotal studies (randomized, double-blind, placebo controlled) conducted in Europe which enrolled 115 patients in 7 centres in Denmark and the UK (Holm-Bentzen et al 1987). Another randomized active-controlled study comparing PPS versus Cyclosporine A was conducted in Europe and published in 2005. This study enrolled 64 patients in 7 Finnish urological units (Sairanen et al 2005). A clinical study conducted in Germany included 58 patients in order to evaluate the safety and efficacy of subcutaneous low-dose heparin application on top of oral PPS application (Van Ophoven et al 2005).

In the Guidelines on Chronic Pelvic Pain, which are released by the European Association of Urology since 2004 (Fall et al. 2004), the oral usage of PPS is recommended as standard treatment for IC already in the first version of these guidelines from 2004. PPS was recommended as standard treatment in this indication in all following updates of this European Guidance up to today (Fall et al., 2008; Fall et al., 2010; Engeler et al., 2012; Engeler et al., 2014; Engeler et al., 2015). In addition, a review article on treatment guidelines for classic and non-ulcer IC from the year 2000 lists oral treatment with PPS as an established treatment option for IC (Peeker et al., 2000).

Several national European patient associations confirmed relevant usage of PPS for the treatment of IC at least since 1996. Respective statements are provided by e.g. the German IC associations and the multinational IC Association covering France, Germany, Belgium, The Netherlands and Austria.

In Germany Pentosan-polysulfat SP54 (25 mg) is commercially available since 1949 and used off-label for the treatment of IC (Sievert et al 2000, recent survey conducted in Germany in 2014-2015 (see also quantitative aspects below).

Furthermore, several publications in German medical literature (textbooks and publications) refer to the usage of Pentosanpolysulfat SP54 for the treatment of IC:

1. Roth, S., Ubrig, B., Semjonov, A., Rathert, P.T. (ed.), Klinische Urologie - Vom Befund zur Therapie, Springer Verlag Berlin, Heidelberg, New York, 2001, Auflage 2

2. Ulrich Kuhlmann, Joachim Böhler, Friedrich C. Luft, Mark Dominik Alscher, Ulrich Kunzendorf (ed.), Nephrologie. Pathophysiologie - Klinik – Nierenersatzverfahren, 6. Auflage 2015 Thieme Verlag

3. Paul Karp, Die Interstitielle Cystitis – ein Leiden zwischen Hoffnung und Frustration, Saarländische Ärzteblatt, Ausgabe 4/2008, pp 14-16

4. Frank Oberpenning, Arndt van Ophoven, Lothar Hertle, Chronische interstitielle Zystitis. Dtsch Arztebl 2002; 99: A 204–208 [Heft 4]

5. Loch, A. & Stein, U.[Interstitial cystitis. Current aspects of diagnosis and therapy]. Urologe A, 2004, 43, 1135-1146.

Further evidence on the systematic and continuous use of PPS for the treatment of Interstitial Cystitis (IC would, as per todays classification, fall under BPS 2X-3C i.e. bladder pain syndrome characterized by either glomerulations or Hunner's lesions) over at least one decade were provided via documented compassionate use usage in France, Norway and the UK (see quantitative aspects of the use of PPS below).

(2) The quantitative aspects of the use of PPS:

For an estimation of the past and current quantitative use in Europe, the Applicant provided the following information about the use of PPS throughout Europe:

- **Germany:**

According to a survey of the health care situation of patients with interstitial cystitis and bladder pain syndrome in Germany conducted in 2010 (Jocham et al 2013) which was based on 270 questionnaires returned by the patients. 42.22% of these patients mentioned that they have been treated with oral PPS.

Another survey conducted by the Market research made by Medimed GmbH revealed relevant off-label use of Pentosanpolysulfat SP54 in 2013-2015: ~4000 prescriptions, assuming 185 treatment courses/12 months, or 1.3% of the potential IC patients in Germany. These prescriptions clearly refer to the diagnostic code ICD N30.1 (chronic Interstitial Cystitis). The diagnostic code, which is used in clinical practice for BPS is R10.2 (Pelvic and perineal pain). The latest data received from IMS Health supplement the data collected by MediMed (MediMed belongs to IMS Health) and confirm a constant off-label use of approximately 2000 prescriptions per year for the treatment of IC (ICD N30.1) (see Table 2).

Table 2 List of off-label use prescriptions of Pentosanpolysulfat SP54 for the treatment of IC

Time period	06/2015-05/2016	06/2014-05/2015	06/2013-05/2014	06/2012-05/2013

ICD N30.1 (chronic Interstitial Cystitis)	1.848	2.010	2.086	2.104

Source: IMS Health, Darwin

Based on the fact that the recommendation to use PPS for the treatment of IC did not change over the last 15 years as demonstrated above by listing different articles and treatment guidelines from 2000 to today, it can be assumed, that comparable off label use of Pentosanpolysulfat SP54 also appeared in the previous years, although the conducted survey just covered the last four years.

- **UK:**

Prescription cost analysis conducted by HSCIC for the years 2003 to 2014 for the treatment of IC (that is not reimbursed), provided information on prescriptions of Elmiron authorised outside the EU for the treatment of IC and PPS 100 mg capsules assuming from 97 to 209 treatment courses of 3 month duration annually, or ~2 to 3% of the potential IC patients in UK. The NHS prescription cost analysis for England 2013 reports that approximately 400 community prescriptions for pentosan were dispensed in 2013.

Table 3 List of PPS prescriptions in the prescription cost analysis of the HSCIC

Year	**Product**	**Delivered capsules**	**Reflect 3-months treatment courses (180 capsules)**
2014	Elmiron	25.400	141
	PPS 100mg	26.700	148
2013	PPS 100mg	28.200	157
	Elmiron	23.300	129
2012	Elmiron_Cap 100mg	25.100	139
	PPS_Cap 100mg	24.900	138
2011	Elmiron_Cap 100mg	30.500	169
	PPS_Cap 100mg	21.100	117
2010	Elmiron_Cap 100mg	33.800	188
	PPS_Cap 100mg	17.500	97
2009	Elmiron Cap	29.900	166
2008	Elmiron Cap	34.500	192
2007	Elmiron Cap	27.200	151
2006	Elmiron Cap	31.500	175
2005	Elmiron Cap	37.600	209
2004	Elmiron Cap	32.600	181

- **France:**

Importation of Elmiron based on single patient prescriptions are handled in France via an "Autorisation Temporaire d'Utilisation nominative" (ATUn). ATUn registrations for the importation of Elmiron authorised outside the EU on single patient prescriptions exist since 2004. According to the ANSM approximately 660 prescriptions for Elmiron were handled via the nominative ATU procedure in France in 2015.

The number of ATU nominatives authorized in France since 2006 are presented in the following. Table 4

Table 4 Number of ATU nominative authorized in France in the indication of IC

ELMIRON 100 mg gelule		
Year	Number of treated patients	Number of new patients
2006	179	109
2007	214	111
2008	240	119
2009	286	132
2010	335	166
2011	373	173
2012	446	197
2013	448	215
2014	427	248
2015	429	227

Approx 10.000 units and more of Elmiron or 330.000 DDD were imported by companies based on individual prescriptions in 2014. The ATU criteria to exclude other diseases were the followings:

- ECBU
- Bladder ultrasound
- Cystoscopy with bladder hydrodistension
- Bladder Biopsy

- **Norway**:

There is information about Elmiron prescriptions in Norway as provided by IMS Health.

Table 5 List of Elmiron prescriptions in Norway from IMS Health

Year	**Units**	**Reflect 3-months treatment courses (180 capsules)**

2004	183	61
2005	196	65
2006	198	66
2007	180	60
2008	168	56
2009	185	62
2010	237	79
2011	231	77
2012	206	69
2013	242	81
2014	229	76
9/15	330	110

IMS Health data provided information about Elmiron prescriptions in the treatment of IC, assuming from 56 to 110 treatment courses of 3 month duration annually, or 7 to 12% of the potential IC patients in Norway.

Next to the use in Germany, UK, France, and Norway, limited information from further European countries documenting the use of PPS for the treatment of IC was found for Poland, Italy and Sweden. In addition, the Applicant provided the quantity of PPS bene pharmaChem GmbH delivered to pharmacies for magistral preparation of PPS in Germany, in Austria and Netherlands from 2003 to 2014. The major part of the supplied drug substance was used as oral preparations for the treatment of IC.

The applicant provided information regarding the dose regimens used in the different European countries. Taking into account treatment recommendations over the last 15 years as demonstrated above by listing different articles and treatment guidelines from 2000 it can be assumed that at least a significant part of the Elmiron prescription was in line with the respective label of the imported products.

Taking into account the rarity of the condition the Applicant has provided sufficient evidence supporting extensive and continued usage of PPS either as Pentosanpolysulfat SP54 or via the US-medicinal product Elmiron for the treatment of IC (bladder pain syndrome characterized by either glomerulations or Hunner's lesions) over more than 10 years in Europe in the claimed indication.

(3) The degree of scientific interest in the use of PPS (as it is reflected in the published scientific literature):

Publications in peer-reviewed journals concerning the epidemiology of Interstitial Cystitis were collected by extensive use of PubMed Central archive at the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM).

To identify relevant studies, the following control terms were used:

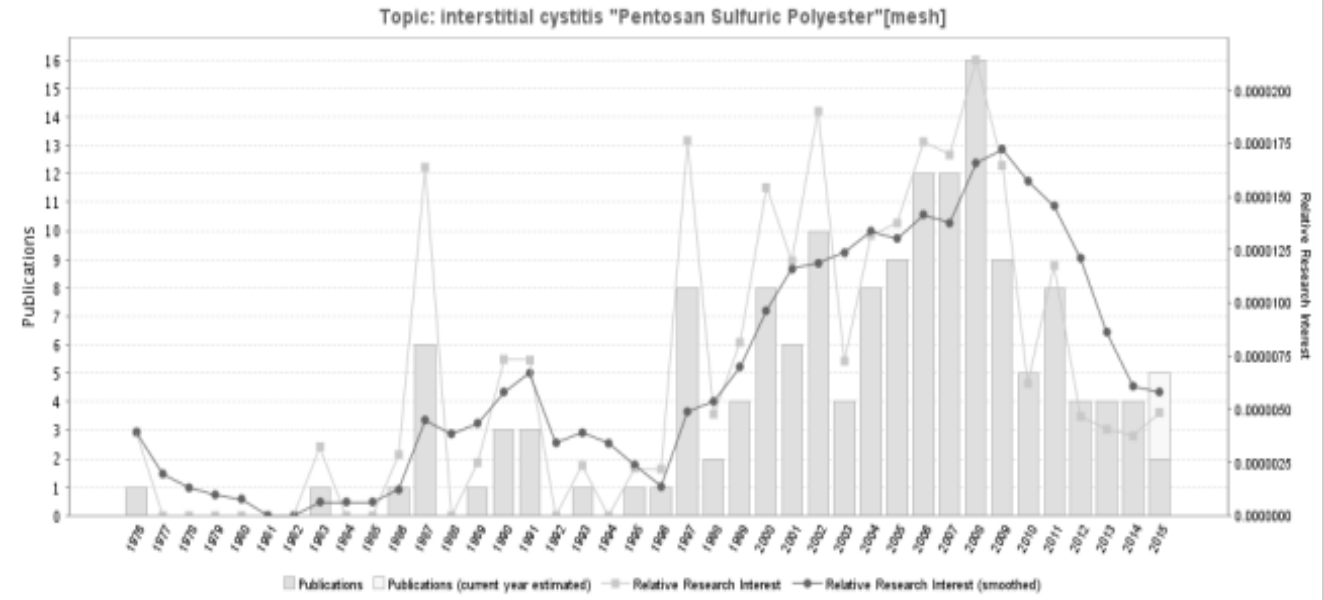
- "cystitis, interstitial" OR ("cystitis" AND "interstitial") OR "interstitial cystitis"

AND

- "pentosan sulfuric polyester" OR ("pentosan" AND "sulfuric" AND "polyester") OR ("pentosan" AND "polysulfate") OR "pentosan polysulfate".

Relevant publications identified after first review of the abstracts were studied in more detail to extract the required information. In addition, relevant references cited in publications identified above were hand searched and evaluated.

The continuous scientific interest in PPS for the treatment of IC is documented by the number of publications over time available on this topic: A review of Pubmed (26.5.2015) identified 2,857 documents found for “Cystitis, Interstitial”[mesh], and 154 adding “Pentosan Sulfuric Polyester”[mesh]. In the following figure GoPubMed (www.gopubmed.org, Transinsight GmbH, Germany) was used to provide chronological information on the occurrence of publications on PPS for the treatment of IC in the MEDLINE database.



- Pubmed database review identified 158 publications from 1978 (32 from Europe), toping to ~15/year in 2008 and ~3/year during last 3 years
- German Institute of Medical Documentation and Information (**DIMDI**) database review identified 209 publications and German National Library of Medicine (**LIVIVO**) database – 197 publications.

The Applicant has undertaken a comprehensive review of the literature published on the use of the product in IC/PBS and found between 158 and 209 publications especially from 1997 to 2014 in the different databases in Europe. The majority of publications were published in North America (86 publications over 158) and 32 publications were published in Europe. The latter are relevant for the demonstration of the degree of scientific interest in the EU. Based on these figures, the degree of scientific interest for PPS was at its maximum in 2006-2008 (14-16 publications/ year) and it still maintains a mean level of about 4-5 publications per year.

Overall, the submitted EU references are considered sufficient evidence of scientific interest in the EU.

(4) The coherence of scientific assessments:

In addition to the efficacy and safety data from the 6 pivotal studies, the meta-analysis, the 9 supportive studies and the safety review from a total of more than 4700 patients which are submitted for evaluation in this application, the Applicant provided all the European recommendations:

- European Association of Urology in their Guidelines of chronic pelvic pain (recommends to use PPS for the treatment of bladder pain syndrome/IC since 2004), the recent guidelines were published in 2015 (Engeler et al 2015) and recommends oral usage of PPS for the treatment of bladder pain syndrome (level 1a)
- Review article on treatment guidelines for classic and non-ulcer IC form year 2000 lists PPS as an established treatment option for IC (Peeker et al 2000),
- Four clinical trials conducted in Europe (Holm-Bentzen et al., 1987; Fritjofsson et al., 1987; Sairanen et al., 2005; and van Ophoven et al., 2005) are not directly comparable but efficacy is consistent with the observations in the studies conducted in the US.

The European Guidelines recommend PPS as standard of care for the treatment of bladder pain syndrome/ IC since 2004 (strong recommendation (A) was given with a grade 1a level of evidence) (Fall et al. 2004) and in all the updated version of these guidelines since 2004 (Fall et al 2008, Fall et al 2010, Engeler et al 2012, Engeler et al 2014, Engeler et al 2015). This is consistent with the recent recommendations of the American association of Urology (Hanno et al 2014) which recommend PPS in second line treatment of PBS after the self-care practices and behavioural modifications (Grade B recommendation). Therefore, PPS is recognized by European and international experts as an effective and safe treatment since more than 10 years.

For conclusion on the scientific assessment please refer to the Benefit / Risk discussion at the end of this report.

(5) The similarity of the claimed formulation to the formulations examined in the literature

The applicant has developed a medicinal product:

- with an active substance quality identical to US Elmiron (same manufacturer)

- with a quantitative composition, with the exception of the capsule shell, identical to the US Elmiron on which are based the clinical studies described in EU (and non-EU) literature.

Formulation and manufacturing process are simple and standard: excipients used are typical for the dosage form, drug substance represents approx. 44% w/w of the total capsule filling weight.

In vitro dissolution results at pH 1.0 4.5 and 6.8 are similar for the PPS drug product and the product used in the literature, both products show a very rapid dissolution >85% within 15 min. Therefore, the profiles can be considered similar in accordance with appendix I of the Guideline on the Investigation of Bioequivalence. The results support the proof of bioequivalence between the medicinal product under application and the product Elmiron used in the literature and fulfil the requirements for a BCS-biowaiver approach for class III drug substances in accordance with appendix III.

Conclusion on the well-established use

As a conclusion of the assessment of the above criteria, the CHMP is of the view that the applicant provides sufficient evidence to establish that the elements related to the quantitative aspects of the use of the substance, the time over which the substance has been used, the degree of scientific interest in the use of the substance in the EU and the coherence of the scientific assessments are

fulfilled. Documentation presented can be considered adequate to show similarity of the drug product with the product used in the publications.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 100 mg of pentosan polysulfate sodium as active substance.

Other ingredients of the capsule contents are microcrystalline cellulose and magnesium stearate. Ingredients of the capsule shell are gelatin and titanium dioxide (E171).

The product is available in HDPE bottle with a tamper-evident PP child resistant closure and PVC/Aclar-Aluminium blisters, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The information on pentosan polysulfate sodium is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of pentosan polysulfate sodium is (1→4)-β-*D*-xylan 2,3-*bis* (hydrogen sulfate) sodium salt corresponding to the molecular formula $(C_5H_6Na_2O_{10}S_2)_n$ and has weight average molecular weight (obtained by light scattering and gel chromatography) of approximately 5760 g/mol and number average molecular weight (the ordinary arithmetic mean or average of the molecular masses of the individual macromolecules) of approximately 3863 g/mol. The polydispersity index is approximately 1.49. Pentosan polysulfate sodium is a semi-synthetic polymer - a heparin-like macromolecular carbohydrate derivative - sulfated polyxylose which chemically and structurally resembles glycosaminoglycans. It has the following structure:

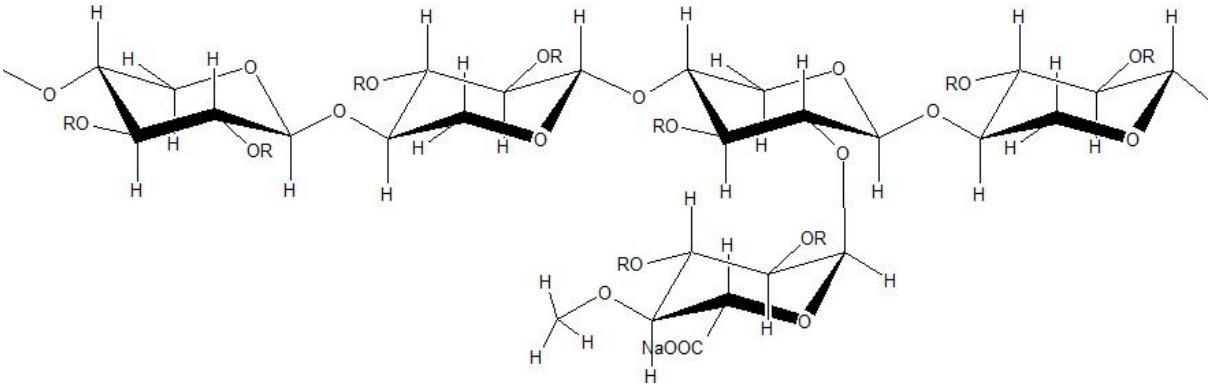


Figure 1 Structural formula of pentosan polysulfate sodium. R = SO_3Na

The structure of pentosan polysulfate sodium was confirmed using a combination of FTIR spectroscopy, XRD, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The molecular weight distribution data was obtained using a combination of light scattering and gel chromatography. Chiral centres of the active substance

originate in the pentosan starting material which is extracted from beech wood. Enantiomeric purity is controlled routinely by optical rotation.

The active substance is a hygroscopic, faintly yellow powder, very soluble in water and insoluble in most organic solvents. Due to very high solubility in aqueous media, control of the active substance particle size is not critical to ensure a consistent performance *in vivo*. Due to low permeability, pentosan polysulfate sodium is classified as BCS-class III substance.

There is no monograph of pentosan polysulfate sodium in the European Pharmacopoeia.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

A single manufacturer carries out the entire process. The active substance is synthesized in 10 main steps using a commercially available well defined starting material with acceptable specifications. At the request of CHMP, additional information about the beech tree plant material used for production of the regulatory starting material was provided, in line with the EMA quality Q&A on semi-synthetic active substances from herbal origin and the relevant Ph. Eur. monographs, thereby ensuring the quality of the active substance. Reprocessing can be performed by repetition of purification steps according to the established manufacturing process in accordance with ICH guideline Q7A.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting material and reagents have been presented. There are no intermediates in the manufacturing process of the active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The proposed packaging materials comply with all applicable requirements.

Specification

The active substance specification includes tests for properties (visual inspection), identity (TLC, visible spectrum spectrophotometry, a further chromatographic method, IR), optical rotation (Ph. Eur.), transparency (Ph. Eur.), refractive index (Ph. Eur.), pH value (Ph. Eur.), viscosity (Ph. Eur.), purity (UV), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), microbiological tests (Ph. Eur.), further inorganic and organic impurities, residual solvents (multiple Ph. Eur. methods) and assay (UV/VIS spectrophotometry and chromatographic methods)

The acceptance criteria of the related substances are in accordance with the ICH Q3A guideline and appropriate specifications have been set.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and identity testing has been presented.

Batch analysis data from 11 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market under long term conditions at 25 ºC / 60% RH and under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

All stability indicating parameters were tested. The analytical methods used were the same as for release.

All tested parameters were within the specifications. No significant changes or trends were observed in any of the parameters tested through storage compared to the initial values.

Photostability testing following the ICH guideline Q1B was performed on one batch. The study confirmed that the active substance is not sensitive to light.

Results under stressed conditions including acidic and alkaline media and heat were provided and it was shown that the methods of analysis used are appropriate to detect the degradation of the active substance, i.e. they are stability indicating. The degradation pathways of the active substance are described and well understood.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as immediate release white hard-gelatine capsules (size 2), each containing 100 mg of pentosan polysulfate sodium.

The aim of pharmaceutical development was to develop a product which is essentially similar to the US product Elmiron, described in scientific literature.

As mentioned above, pentosan polysulfate sodium is a BCS Class III substance exhibiting very high solubility in aqueous media across the physiological pH range and low permeability.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. The compatibility of the active substance and excipients has been demonstrated.

No clinical studies have been submitted. In support of the BCS-based biowaiver approach, the finished product has been compared to the product described in scientific literature by *in vitro* dissolution according to Appendix III of the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev. 1). Comparative dissolution profiles in three different media have been provided and the products are considered similar. The developed dissolution method is in line with Ph. Eur. requirements.

The manufacturing process development is based on blending a powder mixture followed by filling into hard gelatine capsules. The manufacturing process is well known and standard.

The primary packaging is either PVC/Aclar/Aluminium blisters or an HDPE container with child-resistant, tamper-evident PP screw caps. The material complies with Ph. Eur. and EC requirements.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of three main steps: preparation of powder blend, encapsulation and packaging. Conventional pharmaceutical manufacturing equipment is used. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 consecutive commercial scale batches by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and include tests for appearance (visual), identification (IR and a chromatographic method), colour identification for titanium dioxide (colour reaction), average filling weight (Ph. Eur.), filling weight deviation (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), loss on drying (Ph. Eur.), microbiological quality (Ph. Eur.), impurities (chromatographic method) and assay (chromatographic method).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and identity testing has been presented.

Batch analysis results were provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored under long term conditions at 25 ºC / 60% RH, under intermediate conditions at 30 ºC / 75% RH, and under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, identification, dissolution, loss on drying, microbiological quality, impurities and assay. The analytical procedures used are stability indicating.

At 25 °C / 60% RH and 30 °C / 75% RH, all results remained within the proposed specification limits.

At 40 °C / 75% RH after 6 months storage, results were observed for batches packaged in blisters, which indicate that the blisters should not be stored above 30°C.

In addition, bulk capsules, capsules packed in bottles and capsules packed in blisters were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No out of specification results were observed for any of the tested parameters, demonstrating that the finished product is photostable.

An in-use stability study was performed. The results showed no significant changes and a 30 day in-use shelf-life after first opening of bottles is considered acceptable.

Based on available stability data, the proposed shelf-life of 30 months for the bottle and 21 months for blister under storage conditions as stated in the SmPC (section 6.3) is acceptable. The bottles should be kept tightly closed in order to protect from moisture. After first opening the product should be used within 30 days. Blisters should not be stored above 30 ºC.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

No pharmacology studies have been submitted and the Applicant presented literature data. Likewise, pharmacokinetic data are based on 3 main articles dated from 1984 to 2005.

The pharmacological profile of elmiron in the treatment of IC (BPS 2X-3C) is unknown. It is hypothesized, that a potential barrier function of PPS instead of the damaged urothelial mucus might play a role as well the anti-inflammatory activity of PPS. This activity is considered as the likely mechanism of action for the proposed indication.

PPS shows some similarities in its chemical structure as well as in its mechanism(s) of action with unfractionated heparin (UFH), characterized as a sulfated glycosaminoglycan with a mean molecular weight (MW) of about 15-20 kDa (range 2-40 kDa), as well as with low molecular weight heparin derivatives (LMWHs) which are produced by partial depolymerization of UFH exhibiting an average MW of 3-7 kDa. Like heparin, PPS is a mixture of macromolecules but with a higher degree of sulfation and, thus, a higher charge density than UFH. The mean MW of Na-PPS of about 4.7 kDa (80% of the

molecules have a MW between 1.8 and 9.0 kDa) is similar to commercially available LMWHs. However, there are important differences in the structure between PPS, UFH and LMWH resulting in different pharmacodynamic properties.

Parsons showed that PPS resembles the glycosaminoglycans (GAGs) produced by cells in the body, including those lining the bladder (Parsons 1994). Sadhukhan showed a cytoprotective effects resulting in a reduction in the inflammation of the bladder mucosa (Sadhukhan et al. 2002). Chiang et al. demonstrated that PPS appears to inhibit in a dose-dependent manner the stimulation of connective tissue mast cells and mucosal mast cells (Chiang et al. 2000, Chiang et al. 2003) and activated bladder mast cells are reported in patients with IC (Sant et al. 2007).

2.3.2. Pharmacology

Primary pharmacodynamic studies

In Primary Pharmacology part of the dossier, the Applicant presented data from six sources that used studies in vitro and in vivo (with rats and rabbits). In vitro studies by Chiang et al. (Chiang et al. 2000) used peritoneal mast cells isolated from male Sprague Dawley rats demonstrate that PPS may also have an additional or alternate action on bladder mast cells. He demonstrated that PPS has a dose dependent inhibitory effect on mast cell release of histamine induced by the mast cell secretagogue compound 48/80.

The ability of protamine sulfate, an inactivator of the GAG layer (Parsons et al. 1980), to alter membrane permeability to the urinary solute urea, to ionic calcium and to water was examined together with the ability of exogenous PPS to reverse these changes was investigated by Parsons et al. (Parsons et al. 1990). Study supports the hypothesis, that surface polysaccharide play an important role as a bladder permeability barrier in modulating small molecule movement in that its ability to impair such movement can be inhibited by protamine and this protamine effect can be reversed by a treatment with PPS.

Sadhukhan et al. (Sadhukhan et al. 2002) investigated the urothelial cytoprotective action of PPS for treating interstitial cystitis by measuring the activity of the nuclear transcription factor nuclear κB-factor, which is thought to have a role in mediating the urothelial inflammatory response of interstitial cystitis. Authors concluded that PPS might have a nonspecific effect against the viral (dsRNA) and bacterial (LPS) activation of nuclear κB -factor and the observed clinical effect of PPS may be mediated by nonspecific binding of PPS molecules and the inflammatory stimulants of urothelial activation. These findings suggest a mechanism of action for PPS that occurs in the urine rather than at the mucosal membrane by direct interaction of the drug with potential interstitial cystitis inducing inflammatory agents.

Kalota et al. (Kalota et al. 1992) demonstrated that PPS can reduce the damage done by the cytotoxic substance acrolein in transitional cells in the bladder of female rats, which suggests an enhancement of GAG layer properties by PPS. The ability of PPS to reduce toxic effects of acrolein, the active metabolite of cyclophosphamide, and the ability of PPS to improve the bladder's GAG functional layer properties; were highlighted.

Nickel et al. (Nickel et al. 1998) investigated the relative efficacy of heparin, PPS and hyaluronic acid in preventing the absorption of ^{14}C labeled urea in protamine-pre-treated bladders compared with saline-pre-treated control bladders. The results demonstrate that exogenous GAG's are effective in providing an epithelial permeability barrier in protamine-pre-treated bladders.

Secondary pharmacodynamic studies

In the PD Secondary pharmacology section the Applicant overview the historical development of the PPS activity upon blood coagulation, fibrinolysis and lipid metabolism. Barrowcliffe et *al.* (1986) demonstrated after subcutaneous injection of 50mg PPS in humans an enhanced anti·Xa clotting activity and inhibition of the lipid peroxide induced thrombin generation. An increase in plasminogen activator levels after PPS due to the release of endothelial t-PA into the bloodstream was described by Gaffney et al. 1986.

Marsh et al. 1986 reproduced the results in men by evaluating the thrombolytic effect of s.c., i.m. or i.v. injection of 2 - 10 mg/kg PPS in experimental rats. The thrombolytic effect on freshly formed thrombi was demonstrated in the inferior vena cava thrombosis model; the effect was more pronounced in animals allowed to survive for 24 or 48 h.

The anticoagulant and fibrinolytic properties are characteristic of PPS, although its anticoagulant activity is clearly less than that of heparin (Soria et al. 1980, Fischer et al. 1982). The anticoagulant effectiveness of PPS was demonstrated both in vitro and in vivo. The anticoagulant action of PPS is much lower than that of unfractionated heparin which clearly prolonged aPTT, TT and PT as well as inhibited thrombin and FXa activities to nearly the same degree.

The antithrombotic effectiveness of PPS was demonstrated in various experimental thrombosis models in animals. PPS especially prevented the formation of venous thrombi when these were induced by activation of the plasmatic coagulation system due to endothelial damage or injection of activated clotting factors in combination with partial or complete interruption of blood flow. PPS was also effective in arterial thrombosis when thrombus formation was induced by administration of activated clotting factors and stasis, but it was almost ineffective in models of arterial thrombosis when these were mainly based on vessel lesions and activation of platelets. PPS was found to stimulate fibrinolysis *in vivo* in various species due to the release of t-PA from endothelial cells.

Ofosu et al. 1986 concluded from in in-vitro experiments that PPS appear to directly inhibit prothrombin activation *via* several mechanisms (catalysing the inhibition of the initial trace amounts of thrombin formed by heparin cofactor II, direct inhibition of prothrombin activation by the inhibition of the formation of the prothrombinase complex, or inhibition of the expression of the catalytic activity of the prothrombinase complex).

Scully et al. 1986 evaluated the relative potency of PPS for the activation of HC II/thrombin or AT/thrombin interaction in comparison to heparin and dermatan sulfate and to differentiate between high, average and low molecular weight fractions of PPS. Results indicate a coagulation control by PPS principally through inhibition of thrombin mainly (> 80 %) due to HC II.

The effect of PPS on platelet functions is not yet clear. PPS did not affect ADP-induced aggregation and showed only a minor inhibitory activity on collagen- as well as ristocetin induced aggregation but it inhibited the adhesion of platelets to collagen in a concentration dependent manner. The results of the action of PPS on thrombin-induced aggregation are controversial.

PPS aggregated platelets in normal platelet-rich plasma when the aggregation was induced with the serum from patients with documented heparin-induced thrombocytopenia indicating that PPS may provoke immune thrombocytopenia in man.

The anticoagulant efficacy of PPS in vivo (Giedrojc et al. 1999, Barrowcliffe et al. 1988, Doctor et al. 1991, Ofosu et al. 1988) was studied in *ex vivo* samples after s.c., i.v. and i.m. administration into various species such as rats, rabbits and humans. Ex vivo the same inhibitory effects of PPS especially on thrombin and FXa generation can be observed as that seen in vitro, the effects are maintained in

AT-deficient plasma. Significant anticoagulant effects in rats can be observed at parenteral doses of 10 mg/kg and higher, in humans a strong anticoagulant action of PPS is measured in the aPTT assay after s.c. or i.v. administration of doses between 50 and 100 mg. To evaluate the anticoagulant activity of PPS in vivo after different routes of administration the aPTT assay should be used; because of their low sensitivity to PPS TT and PT assays are not suitable and will indicate only a moderate anticoagulant activity of the drug. Comparative studies with PPS and UFH revealed that the overall anticoagulant efficacy of PPS both in vitro and in vivo after parenteral administration is lower than that of UFH.

The comparative measurement of in vitro anticoagulant activities of PPS and UFH demonstrated the strong anticoagulant action of heparin and the relatively low effect of PPS what the Applicant summarises in Table 1. Heparin clearly prolonged aPTT, TT and PT as well as inhibited thrombin and F Xa activities to nearly the same degree. A direct comparison of the anticoagulant effectiveness between PPS and UFH *in vitro* in rats and humans demonstrated an about 10 times stronger action of UFH on the aPTT. Equieffective concentrations of PPS for the prolongation of TT were about 20-40 times higher than that for UFH. PT was least sensitive to both PPS and UFH; equieffective concentrations were about 12 times higher for PPS than for UFH.

Table 6 Comparative anticoagulant actions of PPS and UFH in vitro in human plasma using common clotting assays. Concentrations required for nearly equieffective anticoagulant actions

Assay	PPS	UFH	Reference
aPTT	5.6 µg/ml	0.8 µg/ml	Campbell et al. (1987)
TT	77.5 µg/ml	1.8 µg/ml	Doctor et al. (1991)
PT	124 µg/ml	16 µg/ml	
aPTT	10 µg/ml	1 µg/ml	Doctor and Sauls (1983)
TT	100 µg/ml	5 µg/ml	
PT	200 µg/ml	50 µg/ml	
PTT	12 µg/ml	2 µg/ml	Soria et al. (1980)
TT	75 µg/ml	2 µg/ml	
PT	24 µg/ml	2 µg/ml	
TT	20 µg/ml	1 µg/ml	Vinazzer et al. (1980)
aPTT	20 µg/ml	~ 15 µg/ml	

After oral administration of 400 mg PPS (Fellström et al. 1987) or about 700 mg PPS (Marshall et al. 1997), maximum plasma concentrations in the range of 20-70 ng/ml were observed for unchanged PPS. When total PPS-related radioactivity was assessed after oral administration of 300 mg PPS, Cmax was 250 ng equivalents/ml. Therefore, even at these doses, which are much higher than the intended clinical dose, the concentrations of unchanged PPS obtained in plasma were about 1000x lower than those associated with anticoagulant effects. Even if all metabolites of PPS are taken into account, there is still a safety factor of approximately 100.

Messmore et al. 1989 evaluated the effect of heparin on platelet functions in normal human plasma and correlated this interaction to both the chemical properties such as molecular weight, degree of sulfation, and the inhibitory activity against FXa, thrombin or both.

While heparin markedly suppressed thrombin and collagen aggregation and LMWHs suppressed thrombin-induced aggregation to a modest degree in parallel to their antithrombinactivity, PPS showed no significant inhibition. The collagen-induced aggregation was inhibited by heparin but at only minor degrees by PPS. At very high heparin concentrations (100 units or 600 µg/ml) ADP-induced aggregation was inhibited, PPS and other heparinoids at the same concentrations did not inhibit aggregation by ADP. Ristocetin-induced aggregation was inhibited by heparin and only slightly at high concentrations by LMWHs and PPS. When the aggregation in normal platelet-rich plasma was induced with the serum of patients with heparin-induced thrombocytopenia in the presence of the different compounds studied, besides heparin and LMWHs also PPS at low concentrations of 6 µg/ml showed a positive aggregation effect, whereas at a high concentration of 600 µg/ml the effect became negative. Platelet adhesion to collagen was clearly inhibited by heparin, while PPS was less effective.

Safety pharmacology programme

No safety pharmacology studies with PPS are reported in scientific literature. The available non-clinical and clinical data do not provide any indication of adverse pharmacodynamics effects of PPS on the central nervous system, cardiovascular system or respiratory system.

Since medicinal products based on PPS have been marketed in the USA and in Europe the lack of non-clinical literature in this field is acceptable as superseded by clinical data.

Pharmacodynamic drug interactions

No information on preclinical drug interaction studies conducted with PPS was found in scientific literature.

Since medicinal products based on PPS have been marketed in the USA and in Europe the lack of non-clinical literature in this field is acceptable as superseded by clinical data.

2.3.3. Pharmacokinetics

Several studies have been conducted to evaluate the pharmacokinetics of PPS in humans in healthy volunteers (Fellström et al. 1986, Faaij et al. 1999, Simon et al. 2005, Danielson et al. 1991). Cadroy et al. (Cadroy et al. 1987) determined the pharmacokinetic parameters of PPS in the rabbit from the time course of the plasma TRA concentrations after intravenous injection of 125I-Na-PPS. 5 µCi of 125I-Na-PPS as a marker was injected simultaneously with increasing doses (~ 6 – 12,600 µg/kg) of unlabelled Na-PPS to groups of 2 – 3 animals. The disappearance of the TRA from the plasma of rabbits was triphasic. The half-lives t1/2α (1.8 – 6.8 min) and t1/2γ (3.1 – 5.2 h) as well as the total volume of distribution Vd (180 – 372 ml) were independent of the dose administered. However, there was a highly significant correlation between the dose and the clearance (r = 0.91), and between the dose and the half-life t1/2,β (r = 0.81). The results show that the TRA clearance (Cltot) is reduced (from 17.4 to 4.8 ml/min) and the half-life t1/2β is prolonged (from 15.1 to 41.5 min) with increasing doses. Over the dose range investigated, the clearance varied by a factor of three in the rabbits.

Distribution of radioactivity appeared to be in the whole body after I.V administration in rats with the highest detected radioactivity observed in the urinary tract. Odlind et al. have reported that there were no qualitative differences (only quantitative differences) in distribution in the urinary tract after oral or I.V administration. Dencker and Odlind (Dencker et al. 1985, Odlind et al. 1987) studied the tissue distribution after administration of 3H-Na-PPS in rats. 3H-Na-PPS was administered orally and

intravenously (5 mg/kg) in Sprague-Dawley rats. Detection of radioactivity in the upper intestine suggested some hepatic excretion.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies with PPS are reported in scientific literature which was considered acceptable by the CHMP. The available non-clinical and clinical data do not provide indication of acute toxicity of PPS.

Repeat dose toxicity

In 2-week repeat-dose toxicity studies (no GLP compliance) in mice and rats PPS concentrations of 0, 33, 111, 333, 1000 and 3000 mg/kg were applied via oral gavage once daily for 5 days per week for up to 2 consecutive weeks (National Toxicology Program (NTP) 2004, Nyska et al. 2002). No drug-related mortality was observed. In clinical observations and necropsy: no abnormalities were detected. Some changes were observed in the organ weights. Based on these findings the no observed adverse effect level (NOAEL) was determined: 333 mg/kg body weight for mice males and 1000 mg/kg body weight for females. The NOAEL in 2-week toxicity studies in rats was considered to be 333 mg/kg body weight.

13-week gavage toxicity studies with PPS were conducted in rats and mice. Concentrations of 0, 63, 125, 250, 500 and 1000 mg/kg were applied via oral gavage once daily for 5 days per week for up to 13 consecutive weeks. No drug-related mortality was observed. In these studies were observed increase of body weight in male rats treated with 500 mg/kg. There was also observed an increase in: a) liver weight (in male rats treated with 250 mg/kg or 1000 mg/kg and 500 mg/kg, female rats treated with all dose groups (63–1000 mg/kg), male mice treated with 500 mg/kg, female mice treated with 250 or 1000 mg/kg or 500 mg/kg); b) kidney weight (female rats treated with 1000 mg/kg); c) spleen weight (male rats treated with 125 mg/kg to 1000 mg/kg and 63 mg/kg (absolute), female rats treated with 1000 mg/kg , male mice treated with 1000 mg/kg (absolute and relative) or 125 mg/kg (absolute), female mice treated with 1000 mg/kg); d) lung weight (female rats treated with 1000 mg/kg (absolute and relative) or 125 mg/kg (absolute), female mice treated with 125 or 1000 mg/kg). The observed organ weight increases were associated with the following histopathological observations:

Liver: In both species, hepatocytic vacuolisation was observed in both sexes in the highest dose group and in males in the 500 mg/kg dose group. The characteristic of the vacuolisation was mainly indicative of fat. Inflammation was also observed in male rats treated with 500 and 1000 mg/kg and in nearly all dose groups of mice.

Kidney: In rats, tubular epithelial vacuolisation was observed in both species treated with 1000 mg/kg.

Spleen: In mice histiocytic infiltration was observed in female mice treated with 500 or 1000 mg/kg and in male mice treated with 1000 mg/kg.

Lung: In rats, alveolar histiocytic infiltration was observed in all dose-groups treated with PPS and appeared more severe in the higher dose-groups. Chronic interstitial inflammation occurred in both sexes treated with 500 or 1000 mg/kg and also in females treated with 250 mg/kg.

Rectum: In both species, treatment-related changes consisted of histiocytic infiltration, chronic active inflammation, and chronic ulcers. All observations started with the application of 125 mg/kg to male rats. In female rats, histiocytic infiltration started with the low dose of 63 mg/kg while ulcers and infiltration started with the application of 500 mg/kg only. In male mice, histiocyte infiltration started with 250 mg/kg and ulcer and inflammation started with the highest dose. In female mice, histiocyte infiltration and inflammation started with doses of 500 mg/kg while no ulcers were seen in female mice.

Overall, lesions consisted mainly of infiltration into multiple tissues of vacuolated histiocytes, which, by histochemical investigation, indicated the presence of neutral and acidic mucins and lipidic material within the vacuoles. Transmission electron microscopy identified these vacuoles as lysosomal structures that exhibited a variety of contents. On the basis of these findings, it was concluded, that PPS was absorbed through the focally disrupted rectal mucosa, was deposited in the *lamina propria*, accumulated within macrophages, and then was distributed by these cells or as a free chemical via the lymphatics and blood, to the various organ sites manifesting histiocytic infiltration. The cytoplasmic membrane bound structures within macrophages were lysosomes containing membranous material of cellular origin and, perhaps, remnants of the deposited test material.

Haematological analysis indicated increases for both species in the white blood cells and lymphocyte counts in those animals treated with higher doses of PPS. In both species WBC and lymphocytes were significantly increased in animals treated with 1000 mg/kg.

According results of the studies the no observed adverse effect level (NOAEL) was considered to be: 250 (males) - 500 (females) mg PPS / kg body weight for mice and 125 (males) – 250 (females) mg PPS/kg body weight for rates.

Genotoxicity

Table 7: evaluation of the genotoxic potential

Figure: 1. Type of test / study ID / GLP	**Figure: 2. Test system**	**Figure: 3. Concentrations /** **Figure: 4. Concentration range / Metabolising system**	**Figure: 5. Results** **Figure: 6. Positive / negative / equivocal**
Figure: 7. Gene mutations in bacteria / NTP TR512/ Non-GLP	Figure: 8. Salmonella strains Figure: 9. TA100, TA1535, TA97 and TA98 Figure: 10.	Figure: 11. 0, 100, 333, 1000, 3333 and 10000 µg/mL Figure: 12. +/- S9	Figure: 13. Negative
Figure: 14. In vivo micronucleus test/ NTP TR512/ Non-GLP	Figure: 16. B6CF1 mice (5M / group), F344/N rats (5M / group) micronuclei in	Figure: 17. 0, 156, 313, 625, 1250 and 2500 mg/kg / oral gavage / 3 times at 24 hrs. intervals	Figure: 18. Negative

Figure: 15.	bone marrow cells		
Figure: 19. In vivo micronucleus test/ NTP TR512/ Non-GLP Figure: 20.	Figure: 21. B6CF1 mice (5 / group), micronuclei in PBC	Figure: 22. 0,63, 125, 250, 500 and 1000 mg/kg / oral gavage / 5 d/week for 14 weeks/ incorporated into 3-month toxicity study	Figure: 23. Negative

Genotoxicity studies with PPS. In this NTP Report, genetic toxicity studies were evaluated which derived from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals. The genetic toxicity studies with PPS comprise the following tests (NTP Report): 1. *Salmonella Typhimurium Mutagenicity Test (Ames . Test)* was performed as reported by Zeiger et al., 1987. 2. *Rat and Mouse Bone Marrow Micronucleus Test.* The standard three-exposure protocol is described in detail by Shelby et al., 1993. 3. *Mouse Peripheral Blood Micronucleus Test.* A detailed discussion of this assay is presented by MacGregor et al., 1990. Thus it is concluded that the studies were performed according to international guidelines existing at that time. From the scientific point of view, the results are valid and reproducible and allow a reliable characterisation of the genotoxic potential of the test substance. In line with the evaluation of the NTP Report it is concluded that data derived from the Ames test are valid.

With respect to the question whether the absence of findings in the NTP micronucleus studies could be related to the fact that PPS is poorly absorbed, it can be demonstrated that the animals were maximally exposed to the test substance, because the doses administered were selected on the basis of 13-week maximum tolerated dosage (MTD) studies, in which doses up to 1,000 mg/kg bw were administered. At dose levels of 250 mg/kg and above (rat) and at 1,000 mg/kg (mouse), animals of the 13 week studies developed rectal lesions consisting of chronic ulcers and/or chronic inflammation.

In addition to the outcome of the MTD study, which indicates that PPS is absorbed after oral administration, Abdo et al., 2003 demonstrate that tritiated PPS upon oral administration to Sprague-Dawley rats is absorbed from the gastrointestinal tract and becomes distributed throughout the body (Dencker et al., 1985; Odlind et al., 1987).

Thus, although no toxicokinetic investigations were performed in parallel to the genotoxicity (and carcinogenicity) NTP studies, it can be concluded that the animals were exposed to the test compound.

In agreement with the final conclusion drawn in the NTP-Report, the results of the mutagenicity tests can be summarized as follows: PPS was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, or TA1535 with or without induced hamster or rat liver S9 enzymes. No increases in the frequency of micronucleated polychromatic erythrocytes were seen in bone marrow cells of rats or mice administered PPS by gavage three times at 24-hour intervals. No significant alterations in the frequency of micronucleated normochromatic erythrocytes were seen in peripheral blood samples from male or female mice administered PPS for 3 months by gavage.

Carcinogenicity

Data presented by the Applicant relied on results obtained after oral administration of the US product.Elmiron and are summarized in Table

Table 8: 2-year carcinogenicity studies

Species/Sex/ Number/Group Study ID/ GLP aspects	Dose (mg/kg/d) / Duration /Route	Major findings
Rat F344/ 50/sex/grp **NTP 512 2004 / GLP**	oral gavage once daily / 5 days /week for 104-105 weeks 0, 14, 42 and 126 mg/kg/d (M) 0, 28, 84 and 252 mg/kg/d (F)	Figure: 24. - survival of all dosed groups similar to control Figure: 25. - no effect on mean b.w **Figure: 26. <u>Lung:</u>** Figure: 27. ↑ alveolar inflammation (dose-related) severity minimal-mild / vacuolated histiocytes, neutrophils infiltrates **Figure: 28. <u>Mesenteric lymph node:</u>** Figure: 29. ↑ histiocytic cellular infiltration both sex wherein effect seen ≥ 42 mg/kg/d (M) and ≥ 84 mg/kg/d (F) **Figure: 30. <u>Spleen:</u>** Figure: 31. ↑ lymphohistiocytic hyperplasia (126 mg/kg/d (M) and 252 mg/kg/d (F)./ mild-moderate **Figure: 32. <u>Mammary gland:</u>** Figure: 33. 84 mg/kg/d (F) ↑ incidence fibroadenoma (24/50 vs 15/50 control) but in range of historical control grp ↑ Incidence fibroadenoma, adenolipoma, carcinoma (within historical control grp range) **Figure: 34. <u>Rectum:</u>** Figure: 35. Histiocytic infiltration (126 mg/kg/d for M / 252 mg/kg/d for F)
Mice B6C3F1/ 50/sex/grp **NTP 512 2004 / GLP**	oral gavage once daily / 5 days /week for 104-105 weeks 0, 56, 168 and 504 mg/kg/d	Figure: 36. - survival of all dosed groups similar to control Figure: 37. - no effect on mean b.w (M)/ slight ↓ end study (F) Figure: 38. - no clinical findings **Figure: 39. <u>Liver:</u>** Figure: 40. Hemangiosarcoma (> control) in both sex wherein M more sensitive than F Figure: 41. Hepatocellular adenoma and carcinoma highest dose (M= historical control / F> historical control) **Figure: 42. <u>Spleen:</u>**

		Figure: 43. -malignant lymphoma (F) 504 mg/kg/d, increase incidence related? Figure: 44. - histiocytic cellular infiltration (≥ 168 mg/kg/d (F) / = 504 mg/kg/d (M)) Figure: 45. Adrenal gland Figure: 46. ↑ cortical hypertrophy 504 mg/kg/d (F) **Figure: 47. <u>Rectum:</u>** Figure: 48. Minimal-mild active inflammation, necrosis… more severe for F

NTP conclusions of these 2-year carcinogenicity studies were the following: "Under the conditions of these 2-year gavage studies, there was no evidence of carcinogenic activity* of Elmiron in male F344/N rats administered 14, 42, or 126 mg/kg or in female F344/N rats administered 28, 84, or 252 mg/kg. There was some evidence of carcinogenic activity of Elmiron in male B6C3F1 mice based on increased incidences of liver hemangiosarcoma. The increased incidences of hepatocellular neoplasms in male mice may have been related to Elmiron administration.

There was some evidence of carcinogenic activity of Elmiron in female B6C3F1 mice based on the increased incidences of liver hemangiosarcoma and hepatocellular neoplasms. The increased incidences of malignant lymphomas in female mice may have been related to Elmiron administration.

Elmiron administration caused increased incidences of non-neoplastic lesions (presence of vacuolated histiocytes) of the rectum, lung, mesenteric lymph node, and spleen (males) in rats and of the liver, rectum, mesenteric lymph node, and spleen in mice.

Reproduction Toxicity

PPS does not cross the placental barrier in humans. This is demonstrated in investigations of Forestier et al., 1986 (PPS); Rainaut et al., 1987 (PPS, low molecular heparins (LMWHs); Forestier et al., 1987 (LMWH); Omri et al., 1989 (LMWH); Deruelle and Coulon, 2007 (LMWHs).

In a retrospective study 111 pregnancies under treatment with LMWHs were evaluated by Deruelle et al., 2006; all patients began treatment before the 15th week of pregnancy. The authors conclude that the use of LMWHs for patients requiring anticoagulant treatment from the first trimester appears safe for mother and foetus.

Corresponding results were obtained in experimental animal studies. Andrew et al., 1985 conclude that standard heparin and a LMWH do not cross the placenta in the pregnant sheep. Doutremepuich et al., 1985 compare the passage of commercial heparin and a low molecular weight fragment of heparin across the placenta of rabbits. The authors show that the low molecular weight heparin fraction does not cross the placenta at the dose of 1 000 anti-Xa units/kg. For higher doses (8 000 and 16 000 anti-Xa units/kg) this heparin fraction gives a fetal heparin blood level above that after administration of commercial heparin.

The potential reproductive toxicity of PPS was assessed in Sprague-Dawley rats (NTP, 1997).F0 female and male body weights were unchanged. Body weights of the F_1 high dose group males and females were significantly decreased. Feed consumption values were unchanged. In this reproductive toxicity

study, PPS did not affect reproductive performance. Breeding parameters, fertility, or necropsy endpoints related to reproduction were not altered by the test substance. No differences were noted in epididymal sperm morphology, epididymal sperm density, sperm motility, testicular spermatid counts, or estrous cyclicity.

In the Appendix H of the NTP Technical Report 512 (2004), findings concerning the reproductive tissue and the estrous cycle characterization of rats and mice used in the 3-month gavage studies are summarized. Neither tissue weights (cauda epididymis, epididymis, testis), nor spermatid measurements/spermatid counts and spermatozoal motility nor evaluation of estrous cycle length (days) and estrus stages (diestrus, proestrus, estrus, metestrus) revealed statistically dose dependent differences related to the administration of the test substance.

Data from other repeated dose toxicity studies were evaluated concerning findings which could give any indication for potential effects on male or female fertility. In none of the subchronic or chronic studies in rats and mice an influence on weight development, morphology or functionality of male or female sexual organs could be observed.

Published reproduction toxicity studies are rare. In reproduction toxicity studies in rats which were treated with doses up to 1,000 mg PPS/kg there were no effects on reproductive, breeding, or fertility parameters. Spermatological investigation or evaluation of the oestrus cycles did not reveal any effects of the test compound. Data from other toxicity studies (weights or histologic findings of reproductive organs in males or females) did not give any indication for potential effects on male or female reproduction.

Toxicokinetic data

No toxicokinetic data were not submitted this was considered acceptable by the CHMP.

Local Tolerance

No specific non-clinical local tolerance studies were submitted. This was considered acceptable by the CHMP.

Other toxicity studies

A 28-day repeat dose study to evaluate the potential immunotoxicity of PPS was conducted by NTP (Thakur et al. 2014). Eight female B6C3F1/N mice each were orally administered with PPS at doses of 63, 125, 250, 500 or 1000 mg/kg. For the B16F10 host resistance study, doses administered were 0, 250, 500 or 1000 mg/kg. Each treatment group consisted of 12 animals. The doses, vehicle, and the route of exposure were selected based on the dose levels of the 3-month NTP toxicity studies and to minimize the potential for overt toxicity that could confound immunologic evaluation.

No signs of overt toxicity were observed in the PPS-treated animals. No significant treatment-related effects were observed in mice with respect to body weights except a significant increase (40%) in body weight gain in the 250 mg/kg dose group. The absolute liver weights were increased at the 500 and 1000 mg/kg doses (13% and 23%, respectively) and the relative liver weight was increased at 1000 mg/kg (17%). Treatment-related effects on absolute or relative weights of thymus, spleen, lung or kidney were not observed. PPS treatment resulted in statistically significant increases in the percentage of reticulocytes in the peripheral blood in the 125, 500, and 1000 mg/kg treatment groups (23%, 19% and 29%, respectively).

Erythrocyte numbers, differential leukocyte counts, hemoglobin, hematocrit, MCV, and platelet concentration were not affected.

Mice treated with PPS had a significant increase in absolute numbers of splenic macrophages (63, 500 and 1000 mg/kg) and natural killer (NK) cells (250 and 1000 mg/kg). PPS treatment did not affect the humoral immune response or T cell proliferative response. However, innate immune responses such as phagocytosis by liver macrophages (1000 mg/ kg) and NK cell activity were enhanced (500 and 1000 mg/kg). Further analysis using a disease resistance model showed that PPS-treated mice demonstrated significantly increased anti-tumor activity against B16F10 melanoma cells at the 500 and 1000 mg/kg doses.

The authors conclude, that the current study demonstrated that 28-day PPS treatment enhances the innate immune responses in healthy female B6C3F1/N mice by specifically increasing macrophage and NK cell number, NK cell activity and macrophage phagocytosis.

Consistent with their reported function in host defense, the increases in NK cell and macrophage activity appeared to increase resistance to B16F10 tumor development in mice.

Furthermore, the identified immune potentiating properties of PPS indicates that long term PPS treatment should be used with caution in patients with genetic disposition to development of inflammatory disorders such as autoimmune diseases due to potential exacerbation of innate immune responses.

2.3.5. Ecotoxicity / environmental risk assessment

PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	*in silico*[a]	-0.55	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.03	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			No

An assessment of the ecotoxicity/environmental risk has been conducted by the Applicant. The PECsw was calculated considering the recommended daily dose of 300 mg/day, a Fpen value of 0.0002 which corresponds to the prevalence of interstitial cystitis supporting the Orphan designation of elmiron, and default WASTEWinhab and DILUTION values. The phase I Fpen exceeds the 0.01 µg/L threshold by a 3-fold factor. However, additional studies (phase II) are not considered as necessary since pentosan polysulfate sodium is a carbohydrate derivative which is viewed as unlikely to result in a significant risk to the environment. Although calculated Log Kow values are generally not acceptable (EMA/CHMP/SWP/44609/2010), requesting an experimental determination of Log Kow is not viewed as necessary for the same reason in general. In addition, available data suggest that the Log Kow value of pentosan polysulfate would unlikely reach a value of concern.

Overall, PPS is not expected to pose a risk to the environment.

2.3.1. Discussion on non-clinical aspects

Demonstration of pharmacological activity of PPS in the treatment of IC (BPS 2X-3C) relies on a review of the literature. Although the mechanism of action remains unknown, PPS has shown to be able to bind to bladder epithelium; restore epithelial barrier integrity in bladders with permeability disorders and has anti-inflammatory properties. Moreover, PPS is a low molecular-weight heparin like compound with anticoagulant and fibrinolytic effects. Overall, non-clinical pharmacokinetic data is sparse which is acceptable and evaluation relies on literature and clinical experience.

After I.V. administration of radiolabelled PPS in rabbits clearance of PPS decreased with the dose-increase and this was correlated with a half-life increase. Distribution of radioactivity appeared to be in the whole body after I.V administration in rats with the highest detected radioactivity observed in the urinary tract. Odlind et al. have reported that there were no qualitative differences (only quantitative differences) in distribution in the urinary tract after oral or I.V. administration.

Bioavailability of PPS is weak and absorbed fraction is metabolized in the liver and spleen. Transformation of PPS relies on desulfation process occurring in the liver and the spleen and depolymerisation in the kidney.

As reported by Fellström et al., less than 0.1% of PPS is recovered unchanged in the urine after oral administration in Human, fraction found in the urine are mainly metabolites. PPS is mostly excreted in the faeces (54-84%) as unchanged drug. Overall, pharmacokinetic data regarding the non-clinical field are seldom and assessment should rely on clinical experience.

According to the Applicant, LMWHs and certain heparinoids may be less likely to cause bleeding because they do not interfere with collagen-mediated aggregation and adhesion to a significant degree. However, PPS did show slight inhibitory activity against collagen aggregation and adhesion and it also interacts with the antibody induced by heparin therapy. In accordance with the abovementioned a warning statement on the anticoagulant effects of elmiron was included in Section 4.4 of the SmPC which was considered acceptable by the CHMP.

The toxicological program presented by the Applicant relies on literature review including studies conducted by the NTP on Elmiron. No dedicated acute toxicity study with PPS has been reported in the literature but repeated-dose toxicity studies in rodents have highlighted toxicity localized in lymph nodes (mesenteric and mandibular), liver, lung (only rats), rectum and spleen (only mice).

Elmiron-related increases in organ weight-were observed: lung (rats), liver, kidney (female rats) and spleen (male mice); this in correlation with macrophage infiltration, vacuolization observed in these organs. Ulceration and inflammation localized at the rectum level, is the result of high exposure of this tissue to the drug due to poor absorption after oral administration.

According results of the studies the no observed adverse effect level (NOAEL) was considered to be: 250 (males) - 500 (females) mg PPS / kg body weight for mice and 125 (males) – 250 (females) mg PPS/kg body weight for rates.

Regarding the 2-year carcinogenicity studies, mice are more sensitive towards Elmiron treatment. Increase incidence of neoplastic lesions, with statistical significance, were observed in the liver, malignant lymphoma in the spleen, of B6CF3F1 mouse. Under the conditions of these 2-year studies, PPS was carcinogenic to mice but not to rats.

In the rat carcinogenicity study, there was no substance related increase in the incidence of neoplasms. In the mouse study, increased incidences of liver hemangiosarcoma were related to the administration of the test material (medium and high dose groups males, high dose group females). Additionally, the incidence of liver adenoma was increased (high dose group females). The dosages tested were up to 60 times the maximum recommended human dose (MRHD) in rats, and up to 117 times the MRHD in mice, on a mg/kg basis.
Due to the relevance of the neoplastic findings from the mouse long term study genotoxicity studies have been performed by the National Toxicology Program (NTP) to develop a comprehensive database permitting a critical anticipation of a chemical`s carcinogenicity and are reported in the NTP Technical Report on the Toxicology and Carcinogenesis studies of Elmiron. Results obtained from in vivo genotoxic studies are considered sufficient by the CHMP to demonstrate that PPS is not susceptible of genotoxic damage. Results indicate no mutagenic effect in the Ames Test (in accordance with the OECD guideline number 471) and no consistent increase in the frequency of micro-nucleated polychromatic erythrocytes revealing a mutagenic potential was induced by PPS. Thus, it can be concluded that the findings in the mouse study are not associated with a genotoxic potential and are not applicable to the circumstances in clinical therapy.

Evaluation of PPS impact over the immune system was tested in 28-day repeat dose study and was conducted by the National Toxicology Program (NTP) (Thakur et al. 2014). The doses, vehicle, and the route of exposure were selected based on the dose levels of the 3-month NTP toxicity studies and to minimize the potential for overt toxicity that could confound immunologic evaluation. Treatment-related effects on absolute or relative weights of thymus, spleen, lung or kidney were not observed. PPS treatment resulted in statistically significant increases in the percentage of reticulocytes in the peripheral blood. Mice treated with PPS had a significant increase in absolute numbers of splenic macrophages (63, 500 and 1000 mg/kg) and natural killer (NK) cells (250 and 1000 mg/kg). PPS treatment did not affect the humoral immune response or T cell proliferative response. However, innate immune responses such as phagocytosis by liver macrophages (1000 mg/ kg) and NK cell activity were enhanced (500 and 1000 mg/kg). PPS treatment enhances the innate immune responses in healthy female B6C3F1/N mice by specifically increasing macrophage and NK cell number, NK cell activity and macrophage phagocytosis.

No embryofetal toxicity studies are published for PPS, but indirect evidence of the lack of transplacental passage of PPS was generated via a clinical study published by Forestier (Forestier et al. 1986). Reproduction studies have been performed in mice and rats with intravenous daily doses of 15 mg/kg, and in rabbits with 7.5 mg/kg. These doses are 0.42 and 0.14 times the daily oral human doses of Elmiron when normalized to body surface area. These studies did not reveal evidence of impaired fertility or harm to the foetus from Elmiron. Direct in vitro bathing of cultured mouse embryos with pentosan polysulfate sodium (PPS) at a concentration of 1 mg/mL may cause reversible limb bud abnormalities. Adequate and well-controlled studies have not been performed in pregnant women. The applicant has stated in the proposed SmPC that it is preferable to avoid the use of PPS during pregnancy and should not be used during breast-feeding which is acceptable.

2.3.2. Conclusion on the non-clinical aspects

The Applicant submitted an application for a well-established use product, and as such submitted no new non-clinical data. The scientific literature review of the non-clinical data on pharmacology, pharmacokinetics and toxicology of pentosan polysulfate sodium is considered appropriate to support the proposed clinical use for the treatment of Interstitial Cystitis/ bladder pain syndrome characterized by either glomerulations or Hunner’s lesions in adults.

2.4. Clinical aspects

2.4.1. Introduction

According to Article 10a of Directive 2001/83/EC, if the Applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the EU for at least 10 years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I of the abovementioned Directive, it is possible to replace results of pre-clinical and clinical trials by detailed references to appropriate scientific literature.

Scientific publications of product-specific studies are evaluated which have outlined the efficacy of PPS in comparison to placebo, to other medicinal products or in an uncontrolled fashion. In the case of PPS capsules the information evaluated in this dossier is mainly taken from publications on studies conducted with Elmiron capsules which is the identical medicinal product as the product approved in the US and Canada.

To identify all relevant studies a literature search using the control terms "cystitis" AND "pentosan" was conducted in DIMDI, MedPilot, and PubMed. Relevant publications identified after a first review of abstracts were studied in more detail to extract the required information. In addition, relevant references cited in the publications identified as described were hand searched and evaluated.

First scientific articles describing the efficacy of PPS in this indication were published in 1983. Treatment with PPS is defined as standard of care for the treatment of bladder pain syndrome or Interstitial Cystitis in European treatment Guidelines since the year 2004.

The efficacy of PPS capsules is supported by six placebo-controlled clinical studies as pivotal data. Five of these studies were double-blind, randomized, placebo-controlled clinical studies. In addition one 2x2 factorial study was conducted with PPS and hydroxyzine in a placebo-controlled design (see table “main clinical studies”).

Supportive data on the efficacy and safety of PPS capsules are also provided from uncontrolled studies conducted with PPS capsules as well as from active controlled studies.

Interstitial cystitis / BPS is a disease primarily defined by the symptoms experienced by the patients. There are no established pharmacodynamics biomarkers or histopathological indicators for the severity of the disease. All 6 placebo-controlled studies evaluated efficacy via patient-reported outcome measures as key evaluation tools.

GCP

As this application was submitted under Article 10a (well-established use) it is based on literature. Based on literature only, it is not possible to confirm with certainty whether the studies were performed in accordance with the guidelines and principles of Good Clinical Practices (GCP). Still, some limited information about GCP could be retrieved for the following studies:

Holm-Bentzen 1987: the Helsinki-II declaration was used.

Nickel at al 2015: the study was done in accordance with the ethical principles originating in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent before study participation.

- Tabular overview of main clinical studies

Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoints
Holm-Bentzen et al, 1987	7 centres in Denmark and UK.	Randomized, double blind, placebo-controlled multicentre study	200 mg PPS twice daily or matching placebo for 4 months Study medication was Elmiron	Prospective evaluation of PPS for the Treatment of IC	115 patients Protocol A: 43 patients were randomised, 39 completed the trial : 19 received PPS, 20 received placebo Protocol B: 72 patients were randomised, 66 completed the trial, 33 received PPS,	Protocol A: all patients were female and the median age was 63 years (range 34 to 80 years). Protocol B: 61 women and 5 men were included; the median age was 51 years (range 29 to 78 years)	Clinical and/or cystoscopic evidence of painful bladder disease for at least one year. Protocol A: more than 28 mast cells per mm2 in the detrusor muscle in a bladder biopsy Protocol B: all patients had mast cell counts less than 28/mm2; 3 or more voidings each night and more than 10 points on a defined symptom score scale evaluating the symptoms pain, frequency, nocturia and dysuria).	Efficacy endpoints at month 4: - Symptom evaluation (pain, frequency, nocturia and dysuria) including total symptom score (pre-defined threshold for clinical Relevance: improvement of at least 1,0) - Cystometric first sensation and bladder capacity - Cystoscopic appearance - Cystoscopic maximal bladder capacity - Mast Cell Count

Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoints
					33 received placebo			
Parsons and Mulholland., 1987	2 medical centers in the US	Randomized, double blind, placebo-controlled multicentre study	200 mg twice daily/100 mg PPS three times daily (depending on which institution patients attended) or	Prospective evaluation of PPS for the Treatment of IC	75 patients were randomized; 62 patients completed the study	10% male and 90% female patients. Ulcers were present in 28% of the patients and pain in 75%.	At least one year of symptoms (urgency, frequency, nocturia and/or pain), negative urine cultures, and a cystoscopic examination that showed an ulcer or petechial hemorrhage (after bladder distension), biopsy	Patient-Reported improvement for the four distinct subjective symptoms (urgency, frequency, nocturia and pain) separately 50 % improvement per symptom; no overall evaluation at month 3

Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoints
		Crossover	matching placebo for a minimum of 3 months (treatment was continued for more than 18 months in some individuals) Study medication was Elmiron				proved inflammation and negative cytology studies.	If the patient responded to treatment A, he returned in 3 more months and if there still a positive response, crossover to treatment B
Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
Mulholland et al.,1990	5 centres in the US	Randomized, double blind, placebo-	100 mg PPS three times daily or matching placebo for 3 months (followed by open	Prospective evaluation of PPS for the	110 patients; 56 patients Received placebo; 54	Mean age 43.3 years 91% females 100% white	Urgency expressed as “moderate” on a 5 point analog scale, Frequency of at least 10 voids per day Nocturia of at least 2 voids per night, Pain	Patient Reported Outcome questionnaire based on six point scale global response assessment (GRA) (patients reporting

Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoints
		control led multicen tre study	label extension) Study medication was taken one hour before meals or two hours after meals.	treatment of IC	Patients received PPS	race Placebo: Mean age 45.3 years 87% females 95% white race	as recorded on a 5-point analog scale, Continous duration of symptoms of at least one year, Failed previous conventional therapy such as chlorpactin, hydrodilatation, or DMSO, Average voided volume of 200 ml or less measured over a three day period, Negative urine culture and cytology Cystoscopic examination under anaesthesia (80 cm of water and 1 minute distention) showing petechial hemorrhages or ulcers with gross blood in the fluid return	50% (moderate), 75% (great) 100% (complete cure) improvement overall) at month 3

Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoints
							and a bladder capacity of 800 ml or less.	
Parsons et al., 1993	7 centres in the US	Randomized, double blind, placebo-controlled multicentre study	100 mg PPS three times daily or matching placebo for 3 months. Study medication was taken one hour before meals or two hours after meals.	Prospective evaluation of PPS for the treatment of IC	148 patients were enrolled, 74 in each treatment group; 130 patients completed the study 65/ arm	Mean age 42.7 years 100% females 97% white Placebo: Mean age 45.5 years 93% females 96% white	Anaesthetic bladder capacity (350 – 1,000 cc), Number of voids per day (more than 8) Average voided volume (50 to 200 cc), Nocturia (at least 1 or 2), Patients lacking 1 or 2 of these criteria were entered into the study but they had to have pain and/or moderate urgency, negative urine cytology studies and cultures, and cystoscopic findings of petechial haemorrhages and blood in the fluid return after bladder dilation.	Patient Reported Outcome questionnaire based on six point scale global response assessment (GRA) (patients reporting 50% (moderate), 75% (great) 100% (complete cure) improvement overall) at month 3

Study ID	**No. of study centres / locations**	**Design**	**Study Posology and duration**	**Study Objective**	**Subjs by arm entered/ compl.**	**Gender** **M/F** **Median Age**	**Diagnosis** **Incl. criteria**	**Primary Endpoints**
Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
Sant et al., 2003	13 centres in the US	Rando mized, double blind, placebo-control led multicen tre study 2x2 factorial design	100 mg PPS three times daily or matching placebo or 50 mg of hydroxyzine/ day or combination 50 mg/day of hydroxyzine + 100 mg 3x/day of PPS for 6 months Study medication was Elmiron.	Prospective evaluation of PPS and hydroxyzine for the treatment of IC	136 patients were planned, 121 patients were randomized, 96 patients provided complete follow-up data.	89% females 84% white Median age 45 years	At least 18 years Diagnosis of IC, confirmed by cystoscopy and hydrodistention, following NIDDK criteria (National Institutes for Diabetes and Digestive and Kidney Diseases) Moderate symptoms of urinary frequency (at least 11 times daily) and pain/discomfort (at least 4 on a 0 to 9 Likert	Patient-reported 7-point centred global response assessment (GRA) score as primary efficacy evaluation (patients reporting at least 6 moderately improved or 7 markedly improved on 7 point numerical rating scale)

Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoints
		study					scale) for at least 24 weeks	
Nickel et al., 2015	Total of 67 sites (52 in the US and 15 in Canada)	Randomized, double-blind, placebo-controlled multicentre study	100 mg PPS three times daily or once daily or matching placebo for 24 weeks Study medication was Elmiron.	Prospective evaluation of PPS (300 mg or 100 mg daily) for the treatment of IC	369 eligible patients - 118 patients randomized to placebo, 63 completed - 129 patients randomized to 100 mg PPS, 74 completed - 122 patients randomized	Placebo: 14.4% males 85.6% females 87.3 % white Mean age 44.6 ± 14.58 PPS 100 mg: 7.8% males 92.2% females 84.4 % white Mean age 45.6 ± 15.73 PPS 300 mg: 7.4% males 92.6% females	Men and women of at least 18 years Total score of 8 or greater on ICSI and a score of greater than 0 on each component item (bladder pain, urinary urgency, frequency and nocturia). At least 10 voids per day of which 1 or more were during the night. No intravesical therapy (bladder distension or DMSO) during the 4 weeks before screening. No evidence of microscopic haematuria or evaluation positive for significant urological	The primary endpoint : a responder analysis based on a 30% improvement in the Interstitial Cystitis Symptom Index (ICSI)

Study ID	No. of study centres / locations	Design	Study Posology and duration	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoints
					to 300 mg PPS, 69 completed	84.4 % white Mean age 42.7 ± 15.71	disease within the prior year. No treatment with drugs known to affect IC/BPS symptoms (i.e. antidepressants, antihistamines, antispasmodics or anticholinergics) within the 4 weeks before screening.	

2.4.2. Pharmacokinetics

The composition of the product under application and the product Elmiron authorised in the US for relief of bladder pain or discomfort associated with IC since September 1996 which was used in the literature references is qualitatively and quantitatively identical.

The three studies with PK data are presented below:

Table 1: Main studies with pharmacokinetic data for PPS and summary of the PK data

Mac Gregor et al., 1984 "Metabolism of Sodium Pentosan Polysulphate in Man – Catabolism of Iodinated Derivatives"					
No of study centers / location	Study design	Study drug	Study objective	No of patients	PK results
Scottish National Blood Transfusion Service Headquarters Unit Laboratory', the MRC/SNBTS Blood Components Assay Group2, Edinburgh, the S-E Scotland Blood Transfusion Service' and the Department of Medical Physics and Medical. Engineering', Royal Infirmary, Edinburgh, Scotland, U.K.	PK evaluation	Four subjects were injected intravenously with either 0, 0.1, 1,7 or 50 mg of PPS containing 370 kBq ^{125}I-PPS, one subject receiving tracer alone and tracer plus 50 mg PPS at an interval of 3 weeks. The fifth volunteer was injected subcutaneously with 50 mg PPS containing 370 kBq ^{125}I-PPS.	Evaluate the catabolism of PPS after intravenous and subcutaneous injection in human volunteers and to determine its organ distribution	Five healthy volunteers, weight from 52-77 kg (mean 68) and age from 28-44 years (mean 34).	After i.v. administration of 10.0 MBq ^{123}I-PPS with 1 mg unlabelled PPS images taken at 5 min intervals from 7.5 to 47.5 min showed progressive uptake of ^{123}I by the liver and spleen, such that at 50 min 60% and 7.5% of the dose respectively was associated with these organs. A profile scan at 3 hr post-injection showed 60% of the activity in the liver plus spleen and 13% in the bladder. By 43 hr post-injection the liver plus spleen retention was 37%. Metabolism of ^{125}I-PPS radiolabelled PPS was evaluated via binding affinity to Polybrene in order to detect the desulphation of PPS and gel filtration in order to detect depolymerisation. PPS without affinity to Polybrene was concluded to be macromolecular desulphated PPS. The probable sites of desulphation are the liver and spleen which are rich sources of sulphatases. This assumption is supported by another experiment evaluating the organ distribution of PPS after i.v. administration. Only macromolecular PPS was present in plasma indicating that the kidney is the site of depolymerisation

Marshall et al., 1997 "Phase I Trial of Orally Administered Pentosan Polysulfate in Patients with Advanced Cancer"					
No of study centers / location	Study design	Study drug	Study objective	No of patients	PK results
Lombardi Cancer Research Center, Washington, USA	Phase I trial of p.o. PPS administration in patients with advanced cancer. The initial phase of the study involved a standard dose escalation in cohorts of at least three patients. At the highest dose level achieved, additional patients were enrolled to better characterize the toxicities of this dose and to gather additional biological and pharmacokinetic data at a fixed dose. In four of the patients at the 400 mg/m^2 dose serum samples were taken at 0, 0.5, 1, 2, 4, 6, 8, and 24 h after the morning dose on days 1 and 15.	Dose escalation from 180 mg/m^2 PPS t.i.d to 400 mg/m^2 PPS t.i.d. The drug was applied every 8 hours from day 1 – 56.	To evaluate the Maximum Tolerated dose and generate further PK data on the MTD	21 patients with advanced cancer, of whom 13 patients were enrolled in the initial dose-escalation phase	Summary of pharmacokinetic parameters for PPS: Day 1 / Day 15 C_{max} (ng/ml): 68.7 ± 6.8 / 462 ± 240.8 AUC (ng*h/ml): 987.5 ± 358.7 / 6666.0 ± 3898.7 T_{max} (h): 8.6 ± 10.8 / 4.3 ± 2.4

Simon et al., 2005 "Metabolism of [^{3}H] pentosane polysulfate sodium (PPS) in healthy human volunteers"					
No of study centers / location	Study design	Study drug	Study objective	No of patients	PK results
Ricerca Bioscience LLC, Concord, OH, USA	Single-center, single-dose, open-label study evaluating two groups Collection of plasma samples: 0 (predose), 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0, 36, 48, 72, 96 and 120 h post-dose. Collection of urine samples: 0 (pre-dose), 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120 h post-dosing Collection of faeces samples: 0 (pre-dose), 0-24, 24-48, 48-72, 72-96, 96-120 h post-dosing.	200 µCi [^{3}H]PPS supplemented with 300 mg unlabelled PPS or 300 µCi [^{3}H]PPS supplemented with 450 mg unlabelled PPSformulated in an aqueous solution of 0.9% sodium chloride. The medication was administered in the fasted state.	Evaluation of PK parameters after oral administration of PPS;	Two groups of 8 healthy female volunteers; mean age 39.9 years (22 – 56 years)	Excretion and mass balance in urine and faeces For the low dose group the total recovery of radioactivity after 120 h was 90.43% ± 8.10% (range 73,22 – 97.89%) Approximately 6.30% ± 1.11% (range 4.78 – 7.97%) was excreted in the urine and 84.13% ± 7.71% (range 68.45 – 91.56%) was recovered in the faeces Pharmacokinetic parameters PPS derived radioactivity in plasma (median (CV%): Group 1: C_{max} – 250 ng-eq./ml (25) T_{max} - 2.08 h (180) $T_{½}$ - 26.5 h (23) AUC_{0-120} - 21.0 ng-eq.h/ml (20) Group 2: C_{max} – 358 ng-eq./ml (9.3) T_{max} – 1.83 h (250) $T_{½}$ - 19.5 h (16) AUC_{0-120} – 33.8 ng-eq.h/ml (13) The metabolic profiling with urine indicates that PPS was metabolised extensively by desulfation and depolymerisation, the metabolic profile did not change over time. The faeces contained radioactivity consists predominantly of unchanged PPS.

The other articles mentioned by the applicant for the pharmacokinetic discussion are listed below:

- Danielson et al. (1990) "new drugs to prevent recurrence of renal stone disease", proceedings of XIth International Congress of Nephrology

- Fellström B., Björklund U., Danielson B.G., Erikson H., Odlind B., Tengblad A (1987). "Pentosan polysulphate (Elmiron): pharmacokinetics and effects on the urinary inhibition of crystal growth."

- Forestier, F., A. M. Fischer, F. Daffos, S. Beguin and H. Diner (1986). "Absence of transplacental passage of pentosan polysulfate during mid-trimester of pregnancy." Thrombosis and haemostasis 56(3): 247-249.

• Odlind, B., L. Dencker and A. Tengblad (1987). "Preferential localization of 3Hpentosanpolysulphate to the urinary tract in rats." Pharmacology & toxicology 61(3): 162-166.

Absorption

Fellström et al 1987 and Simon et al. 2005 both showed a very low bioavailability, around or less than 1%. In three-way crossover study of Faaij et al. (1999), 18 healthy male subjects received an i.v. bolus injection of 50 mg PPS, an oral dose of 1500 mg PPS, or placebo; oral bioavailability varied between -0.1 and 0.1% and did not differ from placebo. This conclusion was based in detection of PPS based on effect parameters (APTT and increase of anti-Xa activity as primary parameters. Simon et al., 2005 concluded that PPS was poorly absorbed (bioavailability <1%) in healthy females. This conclusion was based in detection of intact PPS content in urine. In this clinical study healthy female subjects administered a single oral dose of [3H]PPS (200 µCi, <15 mg) + 300 mg unlabelled PPS or [3H]PPS (300 µCi, <15 mg) + 450 mg unlabelled PPS to generate samples containing higher concentration of radioactivity in plasma, urine and faeces for metabolic profiling analysis.

Excretion and mass balance in urine and faeces for the low dose group: the total recovery of radioactivity in 200 µCi dose group after 120 h was 90.43% ± 8.10% (range 73.22-97.89%): Approximately 6.30% ± 1.11% (4.78-7.97%) was excreted in the urine and 84.13% ± 7.71% (68.45-91.56%) was recovered in the faeces (see Figure 4). Thus, the applicant notes that percentage of PPS absorbed was very low. Radioactivity counts in plasma samples were insignificant and variable with median (CV%) peak plasma PPS concentrations of 250 (25) ng-eq/ml and 358 (9.3) ng-eq/ml for lower and higher dose groups, respectively. The peak plasma concentrations were seen at similar time points (~2 h). The Applicant explained that despite that, the fact that about 6% of the administered dose of radiolabelled PPS were excreted via urine shows that absorption takes place and that PPS localizes in the urinary tract after oral administration. This preferential localization was also reported in respective studies conducted in rats (Odlind et al., 1987).

Figure 2 Pharmacokinetic parameters in healthy females following a single dose of oral PPS (Simon et al., 2005)

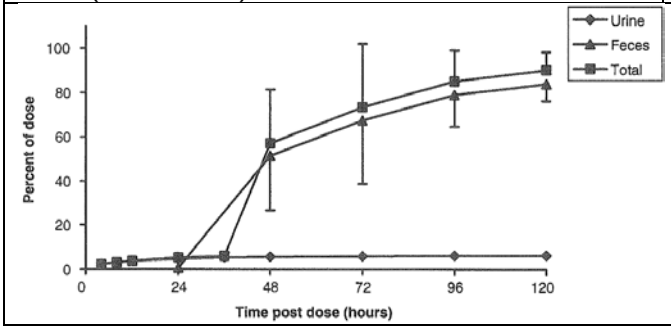
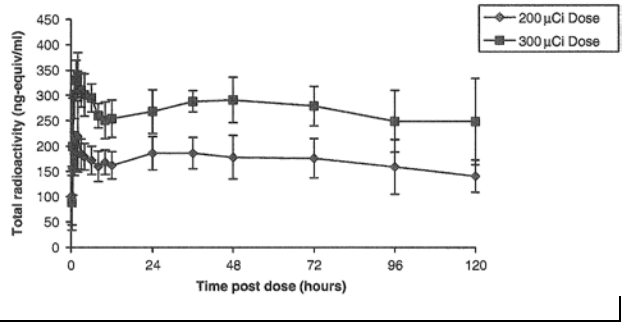
Cumulative excretion of radioactivity in urine and feces (mean ± SD), n = 8	Plasma radioactivity concentrations (mean ± SD) n = 8
	

Table I. Pharmacokinetic parameters for pentosan polysulfate sodium (PPS)-derived radioactivity in plasma.

Parameter	Group 1 200 μCi[3] H-PPS + 300 mg PPS ($n=7$)	Group 2 300 μCi[3] H-PPS + 450 mg PPS ($n=8$)
C_{max} (ng-eq. ml^{-1})	250 (25)	358 (9.3)
T_{max} (h)	2.08 (180)	1.83 (250)
$t_{1/2}$ (h)[a]	26.5 (23)[b]	19.5 (16)[c]
AUC_{0-120} (μg-eq.h ml^{-1})	21.0 (20)	33.8 (13)

Data are medians (coefficient of variation (CV%)).
Plasma concentrations are in ng-eq. ml^{-1}, calculated as disintegrations min^{-1} (dpm)/ specific activity of ^3H PPS (1.48 dpm ng^{-1}).
AUC_{0-120}, area under the curve from 0 to 120 h; C_{max}, maximum plasma concentration; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration.
[a] Estimated based on urinary excretion data. [b] $n=6$. [c] $n=4$.

Distribution

Systemic bioavailability of PPS after oral administration of PPS is very low, accordingly, distribution of PPS was mainly evaluated after parenteral application.

MacGregor et al., 1984

Five healthy volunteers (52 to 77 kg, 28 to 44 years old) were included in the study for this paper. Four subjects received either 0, 0.1, 1, 7 or 50 mg PPS iv with an iode-based radioactive tracer.

Radioactivity was cleared from the blood with a half-live between 13-28 minutes in the lower doses and 45 minutes for the 50 mg dose. Most radioactivity was cleared in a second phase over the next 24-96 hours.

Images taken at 5 minutes interval from 7.5 to 47.5 minutes showed progressive uptake by the liver and spleen. At three hour a profile scan showed 60% of the activity in the liver and spleen, and 13% in the bladder.

Forestier et al., 1986

In the study described by the article, eight women who were going to have an abortion received 50 mg PPS IV. Clinical data (change of coagulation parameters in foetus plasma) provided no indication of transplacental PPS. A potential transplacental passage was evaluated by measuring maternal and foetal coagulation parameters. While in the maternal plasma aPTT was prolonged, factor Xa generation was impaired and factor V level was deeply decreased 30 minutes after intravenous administration of 50 mg PPS, the respective parameters were unchanged in the plasma of the foetuses of the exposed mothers compared to plasma obtained from control foetuses at the same stage of gestation. The data generated in this study provide no indication of transplacental passage of PPS.

Since no further data from clinical studies with PPS in pregnant or nursing women are available, the Summary of Product Characteristics (SmPC) states that PPS capsules should not be used during pregnancy or lactation unless clearly necessary.

Elimination

- **Excretion**

Data generated by **Simon et al., 2005** indicated that the majority of orally administered PPS (84.13% ± 7.71% after 120 h) remained unabsorbed and was excreted predominantly unchanged in the faeces. Radioactivity in the urine consisted mostly of components of lower molecular weight and lower degrees of sulfation than PPS. 6.30% ± 1.11% of the administered dose of radiolabelled PPS were excreted via urine during 120 h after application.

Urine collected over 18 hr after intravenous injection of radiolabelled 125I-PPS contained 35% of the administered activity while stools passed at 18 and 42 hr post-injection contained 0.13% and 0.07% respectively (**MacGregor et al., 1984**).

Radioactivity was detectable in urine within an hour of i.v. injection of 125I-PPS. The recovery of radioactivity in the urine within 24 hr following i.v. injection averaged 31% of the injected dose (range 22-43%) and was not related to the dose of unlabelled PPS (**MacGregor et al., 1984**).

- **Metabolism**

Metabolism of 125I-PPS radiolabelled PPS was evaluated via binding affinity to Polybrene in order to detect the desulfation of PPS and gel filtration in order to detect depolymerisation. PPS without affinity to Polybrene was concluded to be macromolecular desulfated PPS. The probable sites of desulfation are the liver and spleen which are rich sources of sulfatases. This assumption is supported by another experiment evaluating the organ distribution of PPS after i.v. administration. Only macromolecular PPS was present in plasma indicating that the kidney is the site of depolymerisation (**MacGregor et al., 1984**).

In the study conducted by **Simon et al., 2005** a metabolic profiling analysis was conducted in the urine, faeces and plasma samples obtained from three of the high dose subjects. As specific assays for PPS do not exist, metabolic profiling was accomplished through multiple fraction collections and radiochromatographic techniques. The metabolic profiling with urine indicates that PPS was metabolized extensively by desulfation and depolymerisation. The HPLC profiling undertaken with urine samples from selected time-points showed similar HPLC profiles, indicating the metabolic profile did not change appreciably with time. Faeces samples analysed indicated that mainly unchanged PPS is contained in faeces representing PPS amounts that were not absorbed from the GI tract.

Dose proportionality and time dependencies

In Simon et al 2005, after 200 and 300 mg PPS per os, Cmax and AUC were proportional between the two doses. However, as the sample size was small, and no other dose proportionality data are presented, no firm conclusion on dose linearity can be made.

In Marshall et al 1997, after oral administration of PPS three times daily, Cmax increased nearly 7 fold and AUCtau increased nearly 8 fold between D1 and D15. An 8-fold increase in Cmax and AUCtau is consistent with a terminal elimination half-live of 20 hours, which is consistent with the 20 to 24 hours half-live.

According to the accumulation factor R which describes the ratio of Cmax (as well as AUC0-tau, where tau is the dosing interval) between a single dose administration and at steady state, i.e. after multiple administrations, linear pharmacokinetics were assumed. Calculated half-life was 34 hours and the accumulation factor R of 5 to 6.7 must be expected upon repeated dosing of PPS at 8-hours intervals, considering the half-life to be in range between 24 and 34 hours. Oral administration of pentosan polysulfate sodium 3-times daily is expected to lead to accumulation of pentosan polysulfate sodium over the first 7 days of administration (accumulation factor 5-6.7).

Special populations

PK has not been studied in special populations (elderly patients, hepatically or renally impaired patients, paediatric patients, pregnant and breast feeding women), this was considered acceptable with the relevant information included into the SmPC.

Pharmacokinetic interaction studies

No drug-drug interaction study was performed with PPS by the Applicant. Based on one open-label study (Modi et al 2005), the therapeutic doses of PPS have no effect on the pharmacokinetics of R- and S-warfarin or on pharmacodynamics effect as measured by PT, PTT and INR. Besides, the orally administered PPS did not influence aPTT, anti-Xa activity, hepatic triglyceride lipase and lipoprotein lipase in comparison with intravenously PPS or placebo (Faaij et al 1999). There is no expected metabolic drug-drug interaction with desulfation and depolymerisation reactions.

2.4.3. Pharmacodynamics

Mechanism of action

The hypothetic mechanism of action of pentosan polysulfate sodium includes a local effect in the bladder after systemic administration and excretion into the urine by binding of glycosaminoglycans to the deficient mucous of the bladder. This binding of glycosaminoglycans to the bladder mucous bacterial adherence to the cells is reduced by pentosan polysulfate sodium and in consequence the incidence of infections is reduced as well. It is hypothesized, that a potential barrier function of pentosan polysulfate sodium instead of the damaged urothelial mucus might play a role as well the anti-inflammatory activity of pentosan polysulfate sodium.

Primary and Secondary pharmacology

Mainly two potential mechanisms of action are discussed in scientific literature, a repair of defects in the glycosaminoglycan layer and an anti-inflammatory effect of PPS. Respective assumptions on the mode of action are also reflected in the publications on the pivotal studies (Parsons and Mulholland, 1987, Holm-Bentzen et al., 1987, Mullholland et al., 1990). No clinical studies explicitly evaluating potential pharmacodynamics of PPS for the treatment of Interstitial Cystitis were reported in scientific literature, but relevant *in vitro* data with human cells have been generated, which, together with supportive evidence from non-clinical studies reported in scientific literature for the respective hypothesis clearly support the two potential mechanisms of action (please refer to chapter on primary pharmacodynamic studies in the non-clinical part of this report).

Secondary pharmacology

No dedicated studies were performed. The publication of a small PD study on 18 healthy volunteers after administration of oral doses was submitted which evaluated the impact of orally administered PPS on the coagulation system (Faaij et al., 1999). Because no specific assays were available to measure PPS directly during the conduct of the study, indirect measures were used to evaluate the amount of systemically available PPS after oral administration. The evaluated parameters included activated partial thromboplastin time (APTT) and increase of anti-Xa activity as well as measures of endogenous fibrinolysis (tissue plasminogen activator (t-PA) activity and fibrin plate lysis).

The study was carried out as a three-way cross-over bioavailability design, in which 18 non-smoking, normotensive male healthy volunteers received an intravenous bolus injection of 50 mg PPS, and oral dose of 1500 mg PPS or an oral placebo. The wash-out period between the study days was 2 weeks. While the intravenous application of PPS lead to relevant effects on APTT, Anti-Xa activity, t-PA activity and fibrin plate lysis, no such effects were detected after oral administration of the very high dose of 1500 mg PPS applied orally to the subjects.

However as Elmiron post-marketing experience with humans and Nickel *et* al. (2005) data indicate that most common reported AEs were diarrhoea, rectal bleeding and abdominal pain the Applicant was asked to clarify PPS action on GIT providing clear explanation of possible action mechanism, may be related with anticoagulant and fibrinolytic or local irritative properties.

Firstly, the Applicant stated causal relationship of GITs and the administration of PPS is not obvious. GITs are equally reported as associated with the underlying disease and independent of any treatment. According to Van de Merwe, 2006, many patients with IC also have gastrointestinal disorders. A survey in the US in which more than 6.000 IC patients were asked what disorders they had in association with their IC showed following prevalence of associated disorders:

Table 9 Overview of associated disorders in IC patients (van de Merwe, 2006)

	Prevalence (%)	
Diagnosis	**IC**	**General population**
Allergy	41-47	22.5
Irritable bowel syndrome	25.4	2.9
Sensitive skin	22.6	10.6
Vulvodynia	10.9	15.0
Fibromyalgia	12.8	3.2
Chronic fatigue syndrome	7.7	8.5
Migraine	18.8	18.0
Asthma	9.2	6.1
Crohn's disease/ulcerative colitis	7.3	0.07
Thyroid disease	7	?
Rheumatoid arthritis	4-13	1-2
Systemic lupus erythematosus	1.7	0.05
Sjögren's syndrome	8.0	0.5

The author states that it is unclear why patients with IC have these gastrointestinal diseases or disorders more frequently than the general population, apart from similar abnormalities in the movement of the smooth muscle tissue, the type of inflammation process and the occurrence of ulcers.

Gastrointestinal disorders as part of IC were stressed likewise by Jocham et al., 2013. Investigating the care situation of patients with IC in Germany he found that 4.81% of the patients reported gastrointestinal problems as symptoms associated with IC.

The Applicant found an exception in the Marshall et al., 1997 clinical study involving 21 patients with metastatic advanced cancer. Patients were treated with PPS three times per day in cohorts at planned doses of 180, 270, 400, 600 and 800 mg/m^2 body surface in the continuous highest oral dose administered up to almost 2000 mg PPS daily over up to two months. PPS did not cause significant systemic adverse events, but 20 out of total of 21 patients developed moderate to severe gastrointestinal adverse events within 1-2 months at doses of 400mg/m^2 TID.

The PPS dose is estimated to be 3–6 times higher than the recommended dose of PPS used for the treatment of IC. Account should be taken of the fact that the reported gastrointestinal symptoms could likewise be the result of the underlying cancer disease (among others 6 patients with sarcoma, 5 patients with colon carcinoma). It is reported that 14 of the treated patients had completed at least two other treatment attempts before. Possible adequate therapies include radiation therapies which can likewise cause a proctitis with progressive mucosal atrophy from injured micro-vascularisation in the mucosa and submucosal stroma. Furthermore the irradiation of colonic mucosa might decrease prostaglandin production and affect the mucosal permeability to some bile acids causing further destruction and/or alteration of the mucosa eliminating the natural protective barrier of the lower gastrointestinal tract. Thus, the diarrhoea reported might be seen as an attending symptom of the proctitis rather than a side effect of PPS. Further data allowing an assessment of a potential effect of a concomitant therapy as well as to the immunological status are missing.

On the other hand Grigsby et al., 1990 reports of 13 patients, who were treated because of chronic radiation induced proctitis including tenesmus orally with 150 mg up to 300 mg PPS TID. Notably there was no severe acute or chronic toxicity reported in this study, especially no hint on GIT.

Secondly, the Applicant states PK data show that the uptake of PPS following oral administration is low. The impact of orally administered PPS in man on the coagulation system was studied systematically in a bioavailability study by Faaij et al., 1999 proving that the oral administration of 1500 mg PPS (5 times the recommended daily intake) showed no systemic effects on the coagulation system. Thus the Applicant considers it highly unlikely that there is any causal relationship due to the anticoagulant and fibrinolytic properties of PPS.

Thirdly, the Applicant states causal relationship of PPS regarding GITs based on pharmacodynamics and pharmacokinetics is not reported in literature. Therefore, the Applicant presented following reflections:

- Diarrhoea, nausea, dyspepsia and abdominal pain could be due to an osmotic load effect of the PPS created by undigested and/or unabsorbed PPS as well as the cellulose as part of the capsule.
- The degree of sulfatation of PPS might interact with the mucin production GIT causing irritant effects. The gastrointestinal tract is coated by a thick layer of mucus that forms the front line of innate host defence. The mucus consists of high molecular weight glycoproteins called mucins that are synthesized and secreted by goblet cells and functions primarily to lubricate the epithelium and protect it from damage by noxious substances. High degrees of sulfatation of PPS may led to a higher degree of sulfatation in the high molecular weight mucin form and a disturbances in mucin sulfatation process could be detrimental to the maintenance of gastric mucus coat integrity.

2.4.4. Discussion on clinical pharmacology

Absorption

Fellström and al and Simon and al. both showed a very low bioavailability, around or less than 1%. According to Fellström et al., 1987, Marshall et al., 1997 and Simon et al 2005, 6-7% of the administered radioactivity is excreted with the urine and the fraction of unchanged PPS (compared to total radioactivity) is about 1-2% in urine compared to 10-15% in plasma. Therefore, it can be extrapolated that about 1% of the orally administered PPS finally binds to the GAG layer of the urothelium. Considering these pharmacokinetics data, about 3 mg of the unchanged product will reach its target (bladder epithelium) in the urinary tract following a daily oral dose of 300 mg PPS.

The applicant justifies recommending using PPS capsules with water at least 1 hour before meals or 2 hours after meals based on the use the pivotal studies and the efficacy and safety being established for the respective dosing schedule. This was considered acceptable by the CHMP.

Distribution

The reported volume of distribution at steady state reported in Fellström et al was 0.67 ± 0.28 L/kg (for an average 70 kg adult, Vss 46.9 ± 19.6 L). The clearance reported in Fellström et al. was 49.9 ± 6.6 mL/min. Macgregor et al. showed progressive uptake of PPS by the spleen and the liver after i.v. administration. Forestier et al based the absence of trans placental passage of PPS on the absence of clinical signs (change in coagulation parameters).

Elimination and Metabolism

Reported renal clearance was 4.2 ± 1.2 mL/min in Fellström et al. Terminal elimination half-life was 24.1 ± 10.8 hours in Fellström et al; and in Simon et al. it was reported as 26.5 h (CV 23%) and 19.5 h (CV 16%) for 300 and 450 mg PPS respectively. The apparent plasma half-life of pentosan polysulfate sodium depends on the route of administration. While pentosan polysulfate sodium is rapidly cleared from circulation of i.v. administration, the apparent plasma half-life after oral administration is in the range of 24-34 hours.

Simon et al. documented that after oral administration, the majority of PPS was excreted unchanged in faeces, and 6% of the dose was excreted in urine. In Simon et al, radioactivity in urine consisted mostly of components of lower molecular weight and lower degrees of sulfation (indicating PPS was metabolised by depolymerisation and desulfation). Pentosan polysulfate does not exhibit any crystalline structure or polymorphism, so no inter-conversion was expected.

The applicant highlights two studies (Mac Gregor et al., 1984 and Simon et al 2005) that details metabolic pathways. The studies suggest that metabolism take place in liver, spleen and kidneys via desulfation (assumed to be in liver and spleen, which are rich sources of sulfatases) and depolymerisation (concluded as taking place in kidneys, as depolymerised species were found not in plasma but in urine only). This is summarized in SmPC (section 5.2). No specific proportions for metabolism are given which is acceptable, considering rather limited extent of absorption.

Dose linearity and time dependency

In Simon et al 2005, after 200 and 300 mg PPS per os, C_{max} and AUC were proportional between the two doses. However, as the sample size was small, and no other dose proportionality data are presented, no firm conclusion on dose linearity can be made.

In Marshall et al, after oral administration of PPS three times daily, Cmax increased nearly 7 fold and AUCtau increased nearly 8 fold between D1 and D15. An 8-fold increase in Cmax and AUCtau is consistent with a terminal elimination half-live of 20 hours, which is consistent with the 20 to 24 hours

half-live. According to the accumulation factor R which describes the ratio of Cmax (as well as AUC0-tau, where tau is the dosing interval) between a single dose administration and at steady state, i.e. after multiple administrations, linear pharmacokinetics was assumed. Calculated half-life was 34 hours and the accumulation factor R of 5 to 6.7 must be expected upon repeated dosing of PPS at 8-hours intervals, considering the half-life to be in range between 24 and 34 hours. The calculation is appropriate and this information was reflected in the SmPC.

In the pharmacokinetic study published by Simon et al., 2005, inter-individual variability of exposure was relatively low. Coefficients of variation (CVs) of Cmax and AUC ranged from 9.3-25% in this population of 16 healthy women.

PK has not been studied in some of the special populations (elderly patients, hepatically or renally impaired patients, paediatric patients, pregnant and breast feeding women) the lack of this data and precautionary statement are reflected in the SmPC which was considered acceptable by the CHMP.

No drug-drug interaction study was performed with PPS by the Applicant. A causal relationship between PPS und GIT-AEs is not obvious. In case of a causal relationship, most likely local irritant properties as suggested might be responsible regarding an interaction of PPS and mucus. In the context of the side effect rectal bleeding the applicant was asked to summarize the safety of oral PPS and provide additional information from several studies about the risk of rectal bleeding. Based on one open-label study (Modi et al 2005), the therapeutic doses of PPS have no effect on the pharmacokinetics of R- and S-warfarin or on pharmacodynamics effect as measured by PT, PTT and INR. Besides, the orally administered PPS did not influence aPTT, anti-Xa activity, hepatic triglyceride lipase and lipoprotein lipase in comparison with intravenously PPS or placebo (Faaij et al 1999). However, taking into consideration that rectal bleeding is a clinically significant AR and the pharmacological class precautions and warnings referring to a weak anticoagulant effect of PPS were included in the proposed SmPC for PPS and respective information on potential interactions in case of concomitant administration of anticoagulant medicinal products is provided.

No PK/PD profiles of PPS have been investigated by the applicant which is acceptable in this rare indication. Likewise, no clinical pharmacology studies were performed with PPS. Thus, the mechanism of action of PPS is currently not completely understood. It is hypothesized, that a potential barrier function of PPS instead of the damaged urothelial mucus might play a role in the bladder endothelium as well the anti-inflammatory activity of PPS.

2.4.5. Conclusions on clinical pharmacology

A potential weak anticoagulant effect of PPS in patients especially “in patients with an increased risk of bleeding due to concomitant treatments with anticoagulants, heparin derivatives, thrombolytic or antiplatelet agents including acetylsalicylic acid, or non-steroidal anti-inflammatory medicinal products” was adequately reflected in the SmPC.

Regarding the pharmacodynamics, mainly two potential mechanisms of action are discussed in scientific literature, a repair of defects in the glycosaminoglycan layer and an anti-inflammatory effects of PPS. Overall, the studies conducted *in vitro* in human cells supported by relevant non-clinical *in vivo* studies described above provide solid evidence for both mechanisms of action.

However, Pharmacological data of PPS are still lacking in human to better understand the real mechanism of action of PPS in IC / bladder pain syndrome characterized by either glomerulations or Hunner’s lesions in adults. The assessment relies therefore on the evaluation of efficacy in the pivotal trials.

Overall the clinical pharmacology of this product can be considered sufficiently described for the purpose of the marketing authorisation.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

In the two provided supportive dose range evaluations for potential dose-response relationship (Nickel et al., 2005, Nickel et al., 2015) neither 1x100 mg of PPS /day versus 3x100 mg or 2x300 mg, 3x300 mg versus 3x 100 mg of PPS per day leads to statistically significant differences in terms of efficacy.

2.5.2. Main studies

Title of studies
The efficacy of PPS capsules was supported by six placebo-controlled clinical studies as pivotal data. Five of these studies were double-blind, randomized, placebo-controlled clinical studies.

Methods

Study Participants

The enrolled patient population differed between the studies, reflecting understanding and definition of IC at the time, when the study was planned and conducted.

Indeed, there were several agreed definition for IC available in urology among different regions one of the first agreed by **US** National Institute of Health – National Institutes of Diabetes, Digestive, and Kidney Disease (**NIDDK)** in US in 1987, by **International** Continence Society in 2002 (O'Leary-Sant Interstitial Cystitis Symptoms Index **ICSI**), more recently by **European** Society for the Study of IC/BPS (**ESSIC**) in 2008, later by **American** Urological Association (**AUA**) in 2014 and **European** Association of Urology (**EAU)** Guidelines on Chronic Pelvic Pain of the European Association of Urology in 2015.

In particular, ESSIC classification 2X and 3C would meet the NIDDK criteria for IC.

Table 10 ESSIC classification of types of BPS according to the results of cystoscopy with hydrodistension and biopsies

	Cystoscopy with hydrodistension			
	Not Done	Normal	Glomerulations[a]	Hunner's lesion[b]
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive[c]	XC	1C	2C	3C

a Cystoscopy: glomerulations grade 2-3; b Lesion per Fall's definition with/without glomerulations; c Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

Table 11 Inclusion criteria as defined in the six pivotal, placebo-controlled studies

Study	Inclusion criteria
Holm-Bentzen et al., 1987	Clinical and/or cystoscopic evidence of painful bladder disease for at least one year. Additional for protocol A: - More than 28 mast cells per mm^2 in the detrusor muscle in a bladder biopsy Additional for protocol B: - 3 or more voidings per night - More than 10 points on a defined symptom score scale (evaluating the symptoms pain, frequency, nocturia and dysuria)
Parsons and Mulholland, 1987	- at least one year of symptoms (urgency, frequency, nocturia and/or pain) - negative urine cultures - cystoscopic examination showing an ulcer or petechial hemorrhage (after bladder distension) - biopsy proved inflammation - negative cytology studies
Mulholland et al., 1990	- Urgency expressed as "moderate" on a 5-point analog scale - Frequency of at least 10 voids per day - Nocturia of at least 2 voids per night - Pain as recorded on a 5-point analog scale - Continous duration of symptoms of at least one year - Failed previous conventional therapy such as chlorpactin, hydrodilatation, or DMSO - Average voided volume of 200 ml or less measured over a three-day period - Negative urine culture and cytology - Cystoscopic examination under anaesthesia (80 cm of water and 1 minute distention) showing petechial hemorrhages or ulcers with gross blood in the fluid return and a bladder capacity of 800 ml or less.
Parsons et al., 1993	- Anaesthetic bladder capacity (350 – 1,000 cc) - Number of voids per day (more than 8) - Average voided volume (50 to 200 cc) - Nocturia (at least 1 or 2) Patients lacking 1 or 2 of these criteria were entered into the study but they had to have pain and/or moderate urgency, negative urine

	cytology studies and cultures, and cystoscopic findings of petechial haemorrhages and blood in the fluid return after bladder dilation.
Sant et al., 2003	- At least 18 years - Diagnosis of IC, confirmed by cystoscopy and hydrodistension, following NIDDK criteria - Moderate symptoms of urinary frequency (at least 11 times daily) and pain/discomfort (at least 4 on a 0 to 9 Likert scale) for at least 24 weeks before study entry
Nickel et al., 2015	- Men and women of at least 18 years - IC/PBS based on a total score of 8 or greater on ICSI and a score of greater 0 on each component item (bladder pain, urinary urgency, frequency and nocturia) that was unrelated to urinary tract infection for at least 6 months before screening - On average at least 10 voids per day (i.e. 39 or greater voids during three consecutive days, of which 1 or more were during the night (i.e. score of one or greater on ICSI item 3) - No intravesical therapy (eg bladder distension or DMSO) or undergone cystoscopy 4 weeks before screening - No evidence of microscopic hematuria or evaluation positive for significant urological disease within the prior year - No drugs known to affect IC/PBS symptoms (ie antidepressants, antihistamines, antispasmodics or anticholinergics) within 4 weeks before screening

Patients meeting the ESSIC classification 2X to 3C (characterized by either glomerulations or Hunner's lesions were included in four pivotal studies (Parsons and Mulholland 1987, Mulholland et al 1990, Parsons et al 1993 and Sant et al 2003).

Treatments

The main studies were performed with Elmiron capsules, which is the identical medicinal product authorised in the US as the product being applied for in the context of the current application.

The majority of patients in the pivotal studies as well as in the supportive studies were treated with the established dose of 3x100 mg PPS per day and few patients received a dose of 2x200 mg PPS per day. The treatment duration varied from 3 months, 4 months or 6 months.

An overview of the dose-regimens used in the 6 pivotal studies is provided below:

Table 12: Dose regimens used in pivotal studies

Holm-Bentzen et al., 1987	2x200 mg
Parsons and Mulholland, 1987	2x200 mg, 3x100 mg
Mulholland et al., 1990	3x100 mg
Parsons et al., 1993	3x100 mg
Sant et al., 2003	3x100 mg
Nickel et al., 2015	3x100 mg

Objectives

The study objectives of the pivotal studies focused either on IC or IC/BPS treatments.

Outcomes/endpoints

Key study endpoints/outcomes in all 6 pivotal studies were patient-reported outcomes via patient responder analysis. As the definitions for responder analyses were rather heterogeneous, the applicant provided an overview of efficacy endpoints used in the six pivotal studies.

Table 13: Efficacy endpoints of the 6 pivotal, placebo-controlled studies

Study	Efficacy endpoints
Holm-Bentzen et al., 1987	Efficacy endpoints: - Symptom evaluation (pain, frequency, nocturia and dysuria) including total symptom score (pre-defined threshold for clinical Relevance: improvement of at least 1,0) - Cystometric first sensation and bladder capacity - Cystoscopic appearance - Cystoscopic maximal bladder capacity - Mast Cell Count
Parsons and Mulholland, 1987	Symptom evaluation (urgency, frequency, nocturia and pain) 50 % improvement per symptom; no overall evaluation
Mulholland et al., 1990	Primary endpoint: Responder analysis based on 6-point GRA score (patients reporting 50% (moderate), 75% (great) 100% (complete cure) improvement overall) Secondary endpoints: - Investigator evaluation “worse”, “no change”, “fair”, “good”, “very good”, “excellent” - Volume voiding profile over 3 consecutive days (success: decrease 3 or more per day in frequency and an increase of urine volume of at least 20 ml) - Pain & urgency scale (success: at least 1-point improvement)
Parsons et al., 1993	Primary endpoint: Responder analysis based on 6-point GRA score (patients reporting 50% (moderate), 75% (great) 100% (complete cure) improvement overall) Secondary endpoints: - Investigator evaluation “worse”, “no change”, “fair”, “good”, “very good”, “excellent” - Volume voiding profile over 3 consecutive days (success: decrease 3 or more per day in frequency and an increase of urine volume of

	at least 20 ml) - Pain & urgency scale (success: at least 1-point improvement)
Sant et al., 2003	Primary endpoint: Responder analysis based on 7-point GRA score (patients reporting at least 6 moderately or 7 markedly improved) Secondary endpoint: - ICSI score absolute change - ICPI score absolute change
Nickel et al., 2015	Primary endpoint: Responder analysis based on a 30% reduction in patient-reported ICSI score Secondary endpoints: - Responder analysis based on a 50% reduction in patient-reported ICSI score, - Responder analysis based on a 4-point reduction in ICSI total score, - Average bladder pain intensity (11-point numerical rating scale), - Responder analysis based on a 50% reduction in PORIS scale (for pain, urgency and overall assessment), - Responder analysis based on 7-point GRA score (patients reporting at least 6 moderately or 7 markedly improved)

Sample size

In Holm-Bentzen et al, 1987, the minimum number of patients in each protocol estimated before the trial was calculated to 40 on the basis of the following parameters: 2 α = 5% (risk of type 1 error), β = 10% (risk of type 2 error), π1 = 20% (the estimated placebo effect) and π2 = 70% (the estimated drug effect).

In Sant 2003, the projected sample size of 136 participants was selected to detect large differences in response rates of 30% versus 65% (80% power at a 2-sided significance level of 5%). The factorial design provides a savings in overall sample size and is especially useful in studying drugs with non-overlapping mechanisms of effect. However, there is limited statistical power to compare results among individual treatment arms. This trial was intended primarily as a pilot study to evaluate the feasibility of conducting a larger clinical trial. A second objective was to evaluate whether or not there was sufficient evidence of efficacy to warrant expansion to a larger trial. The factorial design combined arms for analysis to increase the statistical power for the main comparisons over that available from comparing individual arms.

In Nickel et al 2015, the target sample size was 645 patients to yield 600 (200 per treatment group) who were evaluable defined as those with 1 follow-up evaluation after baseline. A sample of 215

subjects per group (total of 645) would provide 90% power to detect a 15% difference in the proportion of responders based on ICSI, assuming 30% responders in the active treatment groups and 15% responders in the placebo group.

In Parsons 1987, Mulholland 1990, Parsons 1993, the sample size determination was not mentioned.

Randomisation

In Holm-Bentzen 1987, in both protocols patients were randomized after fulfilling the inclusion criteria and pre-trial investigations to receive either 200 mg sodium pentosan polysulfate or placebo capsules twice daily for 4 months. The interval from cystoscopy to randomization varied but it was not allowed to exceed 4 months. Some patients benefited from dilatation during cystoscopy for 1 to 3 months and they did not start the medication before recurrence of symptoms. The pre-trial symptom score values date from the day the patient began medication.

In Parsons 1987, the patients were randomized to drug or placebo groups by the pharmacy to begin therapy (treatment A). Therapy was begun with 100 mg pentosan polysulfate (or a look-alike placebo) 3 times daily or 200 mg twice daily, depending on institution they attended. At the end of 3 months, if the patient failed to respond to therapy, cross-over to treatment B was begun (from drug placebo or vice versa). If the patient responded to treatment A, he or she returned in 3 more months, and if there still was a positive response cross-over to treatment B was instituted.

In Mulholland 1990, the patients were randomly assigned to PPS or placebo group in accordance with a computer-generated random code providing two parallel groups of patients for comparison.

In Parsons 1993, patients were randomly assigned to receive pentosan polysulfate or placebo in accordance with a computer generated random code providing 2 parallel groups for comparison.

In Sant 2003, 121 participants were randomized by the 7 participating institutions (representing 89% of the goal) over 18 months in equal proportions to the 4 treatment arms using a randomized block design stratified by clinical site.

In Nickel 2015, eligible patients were randomized to PPS 100 mg QD, PPS 100 mg TID (the FDA approved dose) or matching placebo in a 1:1:1 ratio based on a computer generated randomization schedule. Randomization was balanced using randomly permuted blocks and stratified by whether patients had or had not ever been treated with PPS.

Blinding (masking)

All pivotal studies were randomized double-blind according to the authors.

Statistical methods

All six pivotal clinical studies provided a statistical analysis of the efficacy results generated in the respective study:

The efficacy endpoints evaluated in the pivotal placebo-controlled studies were all based on a patient-reported outcome of rather subjective symptoms. In such analyses, the placebo effects are usually rather high. Each of the studies enrolled a very limited number of patients based on the rarity of the disease.

Results

Participant flow

1) In Holm-Bentzen 1987, of the 43 patients in protocol A, 39 completed the study (19 received sodium pentosan polysulfate and 20 received placebo). 4 patients did not complete the protocol A: 2 stopped the medication because of headache, nausea, and dizziness after 1 month and 5 days respectively, 1 was included by mistake and 1 refused to participate. Of the 72 patients in protocol B, 66 completed the study (33 received sodium pentosan polysulfate and 33 received placebo). 6 patients did not complete protocol B: 1 stopped the medication because of a skin rash after 2 weeks, 1 stopped because aggravation of bladder symptoms, 2 refused to participate, 1 was included by mistake and 1 was not followed.

2) In Parsons and Mulholland 1987, of 75 patients randomized into the study, 4 withdrew before they received medication, 9 failed to return to complete the study. Not all patients completed evaluation sheets properly, such that there was no-post-treatment report on urgency in 2 and on frequency in 7. 62 patients completed the study.

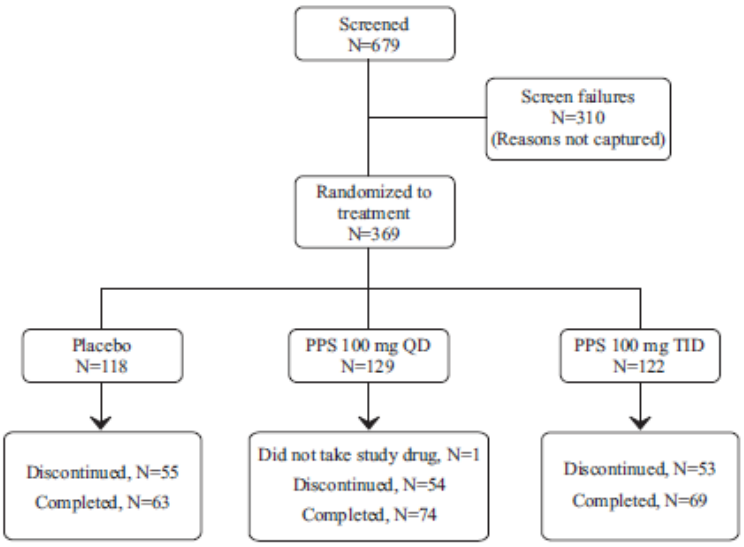
3) In Mulholland et al 1990, 110 patients with documented IC with a duration of one year or more enrolled in the study. Of these, 56 patients were treated with placebo, and 54 were treated with PPS. Twelve patients (3 treated with PPS and 9 treated with placebo) failed to complete the 3 month study. Of these 12, 8 were in the group of patients classified as having severe disease, 1 (3%) receiving PPS and 7 (21%) receiving placebo. Most of these patients were lost to follow-up and it is likely that lack of efficacy was responsible for the patients dropping out. The difference in the drop-out rate between the treatment groups in these patients with severe disease was statistically significant ($p = 0.05$). The treatment was discontinued by 1 patient in the PPS group and 2 in the placebo group due to adverse reactions.

Of the patients who completed the three-month double-blind period, 44% were continuing therapy with PPS one and a half years after the start of the study. These patients had been on therapy for periods ranging from six months to one and a half years.

4) In Parsons et al 1993, a total of 148 patients was enrolled in the study, 74 in each treatment group. A total of 18 patients, 9 in each treatment group failed to complete the 3 month study. Of these patients, 3 in the pentosan polysulfate group and 5 in the placebo group dropped out because of adverse experiences and the remainder were lost to follow-up. It is likely that lack of efficacy was responsible for these latter dropouts. Only 3 patients in the pentosan polysulfate group and 5 in the placebo group discontinued treatment due to adverse reactions.

5) In Sant et al 2003, although recruitment was extended by 8 months, only 121 participants were randomized by the 7 participating institutions, representing 89% of goal. Complete follow-up data obtained in 96 participants (96%). The primary reasons given for withdrawal were adverse events (10of 25, 40%), dissatisfaction with treatment, trial, or symptom changes (7/25, 28%) and other (8/25, 32%).

6) In Nickel et al 2015, the participant flow was the following:



A total of 679 patients were screened and 369 eligible patients were randomized of whom 1 did not receive a dose of study drug. Thus 368 patients were included in the ITT data set. Of the 368 ITT patients, 162 withdrew from study (53 in the PPS 100 mg 3x/d, 54 in the PPS 100 mg/d and 55 patients in the placebo group). Adverse events which were mostly gastro-intestinal, led to the withdrawal of 12 patients (10.2%) in the placebo group, 17 (13.3%) in the PPS 100 mg/day group and 14 (11.5%) in the PPS 100 mg 3x/day.

Recruitment

All but one Nickel et al. (2015) of the 6 pivotal studies were conducted more than 10 years ago.

Conduct of the studies

Studies by Sant et al. (2003) and Nickel et al. (2015) were conducted in the US at a time, when PPS (Elmiron) was commercially available for the treatment of IC. Both studies faced severe recruitment problems, which lead to enrolment of patients, who were previously treated with PPS. The Study by **Sant et al**. (2003) amended exclusion criteria in order to improve recruitment. Initially the study excluded patients who had been previously treated with ≥100 mg TID oral PPS for ≥12 consecutive weeks. This criterion was amended to an exclusion of PPS treatment during 4 weeks prior to the study; 15/121 patients (12%) were randomized before this amendment.

The study by **Nickel et al**. (2015) was terminated earlier despite numerous efforts to promote recruitment. A higher than expected response rate noted in a blinded analysis of study data in 2009 (44% vs the 25% response rate used in the sample size calculation) combined with the slow enrolment led to the interim analysis of study data by individuals uninvolved in study performance. These results prompted **early termination** of the study. Futility assessment revealed that continuing the study until its planned sample size may have taken up to additional 5 years, and would not have increased significantly the chance of a successful trial.

Baseline data

A total of 413 patients were exposed in the reported pivotal studies to PPS in the recommended dose of 300 mg per day (or a very comparable dose of 400 mg per day), the majority of these patients were Caucasian, female and the average age was above 40 years:

1) The study reported by Holm-Bentzen et al., 1987 was conducted in 7 centers in Denmark and in the UK. Nineteen patients were exposed to PPS and 20 patients received placebo in protocol A while in protocol B, 33 patients were enrolled in each group. In protocol A, all patients were female and the median age was 63 years (range 34 to 80 years). The median duration of the disease was 7 years with a range of 1 to 50 years. In protocol B, 61 women and 5 men were included; the median age was 51 years (range 29 to 78 years). The median duration of the disease was 6 years with a range of 1 to 51 years.

In both protocols, patients were randomized after fulfilling the inclusion criteria and pre-trial investigations. All patients studied had had clinical/or cystoscopic evidence of painful bladder disease for at least 1 year and repeated negative urine cultures. The interval from cystoscopy to randomization varied but it was not allowed to exceed 4 months. The pre-trial symptom score values was evaluated from the day the patient began medication by the symptom scale.

Besides, the mast cells in the detrusor muscle were counted in 2 separate biopsies from each patient by the same observer.

In protocol A, the fulfilment of a pathological anatomical criterion for IC was necessary (> 28 mast cells per mm^2 in the detrusor muscle in a bladder biopsy).

In protocol B, no definite pathological anatomical criteria were obtained but all patients had mast cell counts < 28/mm^2.

The majority of patients have petechial bleeding at baseline (15/19 in protocol A and 24/33 in protocol B), but a relevant (39%) proportion had no petechial bleeding at baseline.

2) No clear information is provided on the patient demographics of the study reported by Parsons and Mulholland, 1987, which was conducted in the US in 2 medical centers. Based on the results, 62 patients were exposed to PPS in this study with 10% male and 90% female patients.

Patients were eligible have at least one year of symptoms, consisting of urgency, frequency, nocturia and/or pain, negative urine cultures, a cystoscopic examination that showed an ulcer or petechial hemorrhage (after bladder distension) and negative cytology studies. Ulcers were present in 28% of the patients at baseline and pain in 75%. There were no abnormal serum tests, including prothrombine time, partial thromboplastin time, lactic dehydrogenase, serum glutamic oxaloacetic and pyruvic transaminases, haematocrit or white blood count. Micturitional profiles were obtained in some patients but not in all. These profiles were done before the study and at each visit and consisted of a 3-day recording of each voided volume from which the average voided volume of daily voids could be determined.

3) Of the 110 patients enrolled in the clinical study reported by Mulholland et al., 1990 54 patients were treated with PPS (mean age 43.3 years, 91% females, 100% Caucasians) and 56 patients were treated with placebo (mean age 45.3 years, 87% females, 95% Caucasians). The baseline characteristics are mentioned in the table 8 below.

Table 14 Patient characteristics at baseline

Parameter	PPS	Placebo
Patients		
Mean age (yrs.)	43.3	45.3
Females (%)	91	87
White race (%)	100	95
Mean duration of disease (yrs.)	7.4	5.8
Cystoscopic findings		
Bloody fluid return (%)		
Mild	31	27
Moderate	39	46
Severe	30	27
Fissures (%)		
None	6	7
Few	28	29
Moderate	40	35
Many	26	29
Petechial hemorrhages (%)		
Few	26	27
Moderate	46	48
Many	28	25
Hunner's ulcer present (%)	8	4
Other abnormalities present (%)	4	11
Mean bladder capacity (cc)	569	585
Patients with severe disease (%)	59	59

It should be noted that the study design was a double-blind placebo-controlled. The patients were randomized to drug or placebo groups by the pharmacy to begin therapy (treatment A). Therapy was begun with 100 mg pentosane polysulfate (or a look-alike placebo) 3 times daily or 200 mg twice daily, depending on which institution they attended. At the end of 3 months, if the patient failed to respond to therapy, cross-over to treatment B was begun (from drug to placebo or vice versa). If the patient responded to treatment A, he or she returned in 3 more months and if there still was a positive response cross-over to treatment B was instituted. To complete the study, the patient had to fail arms A and B, or to have 2 successive visits (6 months) with a positive response.

Patients were categorized in terms of the severity of their disease. Patients with a moderate degree of disease were defined as having anesthetic bladder capacity over 400 ml, 18 or fewer voids per day, and an average voided volume of 75 ml or more. Patients were considered to have a severe degree of disease if they had bladder capacity under anesthesia of less 400 ml, or more than 18 voids per day, or an average voided volume of less than 75 ml. A patient with any one of these three criteria was included in the severe group. Anesthesic bladder capacity was measured under 80 cm of water pressure held for one minute in all patients under general or spinal anesthesia (see table 8 “patients’ characteristics at baseline”).

4) The US-study reported by Parsons et al., 1993 enrolled 74 patients in each group, all of whom had documented IC of at least 1 year in duration. The mean age was 42.7 years in the PPS group and 45.5 years in the placebo group. All patients in the PPS group were female and 93% of the placebo-treated patients were female. The vast majority of patients were Caucasians (97% in the PPS group and 96% in the placebo group). It was a prospective double-blind, placebo-controlled study conducted at 7 clinical centers on 148 patients for a treatment period of 3 months.

Table 15 Patient characteristics at baseline

Parameter	Pentosanpoly-sulfate	Placebo
Mean age (yrs.)	42.7	45.5
% Women	100	93
% White pts.	97	96
Mean duration of disease (yrs.)	6.6	6.6
% Cystoscopic findings:		
Bloody fluid return:		
Mild	18	15
Moderate	36	37
Severe	46	47
Fissures:		
None	3	4
Few	7	8
Moderate	42	47
Many	49	41
Petechial hemorrhages:		
None	1	1
Few	9	8
Moderate	41	43
Many	49	47
Hunner's ulcer present	4	4
Other abnormalities present	11	8
Mean bladder capacity (cc under anesthesia)	656	601

There were no significant differences between the treatment groups at baseline in terms of age, sex, distribution, race, duration of disease, cystoscopic findings or bladder capacity.

5) The factorial design study reported by Sant et al., 2003 was conducted in the US and enrolled 4 groups of patients:

. Placebo group: 31 patients; mean age 41.6 ± 15.5 years; 90% females, 94% Caucasians,

. Hydroxyzine group: 31 patients; mean age 47.8 ± 13.9 years; 84% females, 84% Caucasians,

. PPS group: 29 patients; mean age 48.7 ± 15.1 years; 90% females, 72 % Caucasians,

. Combination group: 30 patients; mean age 43.7 ± 15.1 years; 93% females, 87% Caucasians.

Table 16 Baseline patient characteristics by treatment group

Characteristic	Placebo	Hydroxyzine Alone	PPS Alone	Combination Therapy
No. randomized	31	31	29	30
No. female (%)	28 (90)	26 (84)	26 (90)	28 (93)
No. race (%):				
White	29 (94)	26 (84)	21 (72)	26 (87)
Black	0	2 (6)	4 (14)	2 (7)
Hispanic	0	2 (6)	3 (10)	1 (3)
Other	2 (6)	1 (3)	1 (4)	1 (4)
No. prior symptoms 52 or more wks (%)	29 (94)	30 (97)	28 (96)	27 (90)
Mean age ± SD	41.6 ± 15.5	47.8 ± 13.9	48.7 ± 15.1	43.7 ± 15.1
Mean pain score ± SD (0–9)*	6.0 ± 1.3	6.0 ± 1.0	6.3 ± 1.4	5.8 ± 1.1
Mean urgency score ± SD (0–9)*	6.5 ± 1.5	6.7 ± 1.4	6.9 ± 1.2	6.1 ± 1.4
Mean 24-hr frequency ± SD†	18.9 ± 10.3	19.9 ± 6.3	18.3 ± 6.8	16.5 ± 8.0
Mean IC symptom index ± SD (0–20)	14.6 ± 3.3	14.1 ± 3.7	14.3 ± 3.3	13.3 ± 3.5
Mean IC problem index ± SD (0–16)	12.8 ± 2.4	12.9 ± 2.9	12.8 ± 2.7	11.8 ± 2.5
Mean Wisconsin IC score ± SD (0–42)	32.9 ± 6.7	32.3 ± 7.8	30.4 ± 6.8	28.4 ± 8.5‡

* Average of 2 baseline scores.
† A statistically significant difference in baseline frequency among treatments (p = 0.0037).
‡ A subject on the combination arm was missing baseline University of Wisconsin IC score data.

6) The latest study reported by Nickel et al., 2015 enrolled 122 patients in the US (mean age 42.7 ± 15.71; 92.6% females, 84.4% Caucasians) in the PPS 300 mg group, 128 patients (mean age 45.6 ± 15.73; 92.2% females, 84.4% Caucasians) in the PPS 100 mg group, and 118 patients (mean age 44.6 ± 14.58; 85.6% females, 87.3% Caucasians) in the placebo group.

Table 17 ITT data set demographic and baseline characteristics, efficacy at study end points and treatment emergent adverse events in 5% or more of patients

	Placebo		PPS 100 mg QD		PPS 100 mg TID	
No. pts	118		128		122	
No. male (%)	17	(14.4)	10	(7.8)	9	(7.4)
No. female (%)	101	(85.6)	118	(92.2)	113	(92.6)
No. race (%):						
White	103	(87.3)	108	(84.4)	103	(84.4)
Black	6	(5.1)	5	(3.9)	8	(6.6)
Asian	1	(0.8)	1	(0.8)	5	(4.1)
Hispanic	7	(5.9)	9	(7.0)	5	(4.1)
Other	1	(0.8)	5	(3.9)	1	(0.8)
Mean ± SD age/median (range)	44.6 ± 14.58/44.0	(18–78)	45.6 ±15.73/44.0	(18–87)	42.7 ± 15.71/42.0	(19–85)
Mean ± SD kg/m^2 body mass index/median (range)	27.0 ± 6.50/25.7	(17.1–45.4)	26.7 ± 9.45/25.3	(17.6–115.5)	27.1 ± 11.02/24.7	(16.8–129.8)
Mean ± SD ICSI total score/median (range)	13.8 ± 3.06/14.0	(7–20)	13.4 ± 3.01/13.0	(7–20)	13.3 ± 3.12/14.0	(8–20)
Mean ± SD pain intensity scale/median (range)	5.2 ± 2.25/5.0	(0–10)	4.7 ± 2.25/5.0	(0–10)	4.7 ± 2.25/5.0	(0–10)
Daily urinary frequency:						
No. pts	107		117		110	
Mean ± SD No./median (range)	16.0 ± 7.79/14.3	(9–77)	14.8 ± 4.01/13.7	(9–31)	14.7 ± 4.02/13.8	(10–35)
No. PPS naïve (%)	97	(82.2)	102	(79.7)	106	(86.9)

The majority of patients were Caucasian, female and the average age was above 40 years. Although, 5/6 pivotal studies were conducted in the US, the majority of the patients enrolled were Caucasians and are representative for the EU population.

Outcomes and estimation

1) Primary efficacy analysis

Holm-Bentzen et al. (1987): ***no clinically significant difference*** between PPS and placebo was found for the median pre-trial and post-trial values for the total symptom score in protocols A and B. For protocol A the decrease was 0.625 in score values in both groups, while for protocol B the decrease was 0.50. The decreases in total symptom score compared to baseline were statistically significant in both protocols. A clinically significant improvement was pre-defined as a decrease of at least 1.00 in the mean total symptom score per patient. A responder analysis evaluating the number of patients experiencing clinically significant improvement revealed a trend for higher responder rates under treatment with PPS compared to placebo (6 vs. 4 responders in protocol A and 9 vs. 7 responders in protocol B). Authors concluded that PPS was not superior over placebo in the treatment of painful bladder disease.

Parsons and Mulholland (1987): Responder analysis (number of patients experiencing at least 50% improvement per symptom) on the four symptoms evaluated (pain, urgency, frequency and nocturia). Evaluation of all available patient data after cross-over showed that PPS was ***statistically***

significantly (*p<0.05*) more effective than placebo in reaching improvement of all subjective symptoms (pain, urgency, frequency and nocturia). Voided volume showed a tendency towards significant increase (***p = 0.06***).

In this study there was no overall evaluation of the symptoms. Patients who responded to therapy showed improvement at 5 to 10 weeks and continued to improve during several months. Remission of disease tended to be long-term. Of 25 individuals treated for more than 18 months (in an open-label once they completed the study) only one broke through therapy. When the drug was terminated the disease reappeared within 3 to 12 weeks in 80 percent of these patients.

Mulholland et al. (1990): In this three month study 28% of patients treated evaluated themselves at the end of the treatment period as more than slightly improved relative to baseline; compared to 13% of the patients treated with placebo (***p=0.04***)**.**

Parsons et al. (1993): At the end of the three months treatment period 24 of 74 PPS treated patients (31%) evaluated themselves as at least 50% overall improved relative to the condition at the beginning of the study compared to 12 of 74 patients in the placebo group (16%) (***p=0.01***).

Sant et al. (2003): In this study, the main treatment effect of PPS was evaluated by combining data from the placebo and hydroxyzine alone arms and comparing those to data from the PPS alone and PPS plus hydroxyzine combination arms. A responder analysis based on a patient-reported Global Response Assessment (GRA) at 24 weeks was defined as primary endpoint. The study did not enrol the planned patient number and the rather high number of drop outs during the study. A trend (***p= 0.064***) for better efficacy was observed in those patients treated with PPS (20 of 59, ***34%***) compared to the non-PPS group (11 of 62, ***18%***).

Nickel et al. (2015): The primary efficacy results of this study were a responder analysis based on a 30% improvement in the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) at week 24. The primary analysis in the reported study was conducted on a last-observation-carried forward (LOCF) basis, for those patients who withdrew before completing the 24 weeks. There was ***no statistically significant difference*** between the different treatment groups for the primary endpoint pre-specified analysis of the ITT data set. The responder rates were 40.7%, 39.8% and 42.6% for the placebo, PPS 100 mg and PPS 300 mg group, respectively. The percent of responders was similar for PPS naïve and non-naive patients across all 3 treatment groups. A *post-hoc* subgroup analysis of the 94 patients meeting the NIDDK criteria revealed a 50%, 30.3% and 34.5% responder rate for the respective treatment groups.

The authors explained that the differences in this study compared to the earlier studies of Mulholland et al (1990) and Parsons et al. (1993) are based on (1) differences in the enrolled patient population (current study enrolled with milder symptoms, no cut-off criteria for pain or urgency, no determination of flare status, no entry criterion based on cystoscopy findings and no exclusion for commonly associated conditions such as irritable bowel disease, depression or pelvic floor dysfunction disease) and (2) on the commercial availability of PPS, which lead to slow recruitment into the study and to early termination; it might have resulted into a different population of patients who agreed to participate, including those who were not PPS naïve and who were non-responders to previous PPS therapy or potential non-responders based on disease phenotype.

2) Secondary efficacy analysis

1) In Holm-Bentzen et al 1987, the effect of treatment in the individual patient was expressed as a decrease of 1 or more numerical values in symptom score for pain, dysuria, frequency and nocturia.

Regarding the other efficacy endpoints (frequency, nocturia, pain, dysuria, maximal bladder capacity during anaesthesia, petechial bleeding, first sensation and bladder capacity, mast cell/mm^2 in the biopsies in protocol B, again **no significant difference** was found between the PPS and placebo groups.

However, for protocol A, there was a statically significant increase in bladder capacity (from 260 to 475 ml) in the patients treated with PPS compared to placebo ($p< 0.05$). The bladder capacity in the placebo remained constant. For protocol A, there was a statistically significant decrease in the mast cell count during the trial ($p< 0.01$).

2) In Parsons and Mulholland 1987, the micturitional profiles' results are reported in table 21.

Table 18 Average number of daily voids and bladder volumes determined by micturitional profiles

	Placebo	Drug
No. pts.	29	34
Av. No. daily voids:*		
Before therapy	20.1 ± 9	18.9 ± 9
After therapy	20.8 ± 13†	18.3 ± 10‡
Net difference	0.7	−0.6
No. improved (%)	6 (21)	13 (38)
Av. voided vol. (ml.):§		
Before therapy	80.4 ± 42	85.2 ± 46
After therapy	84.6 ± 53‡	102.5 ± 57‖
Av. change	4.2	17.3

P values were determined by Student's t test. Each group represents the patients who were evaluated after cross-over, such that some received drug and placebo therapy.

* Net difference represents the difference in voids per day before and after therapy. Number improved is the number of subjects with at least 3 less voids per day. In regard to this factor the drug did better than the placebo ($p = 0.1$).

† $p = 0.6$.

‡ $p = 0.5$.

§ There was a significant increase in bladder capacity in the drug group ($p = 0.009$) but not in the placebo group.

‖ $p = 0.009$.

The average voided volumes were significantly improved on drug therapy (**p = 0.009**) but not on placebo. The average number of voids per day was unchanged after drug or placebo therapy. The micturitional profiles showed significant improvement in average voided volumes but not in average daily voiding episodes.

3) In Mulholland et al 1990, in terms of reduced pain, 27% pf the PPS patients evaluated themselves as improved compared with 14% of the placebo patients ($p =0.08$). This was confirmed by the pain scale data where 46% of the PPS patients and 29% of the placebo patients recorded a decrease in pain of 1 or more ($p= 0.07$). The mean reduction in pain from baseline as measured by the pain scale was 0.5 for the PPS-treated patients compared with 0.2 for the placebo patients at three months. This difference between the treatment groups was not significantly but the difference from baseline was significantly different from zero ($p = 0.05$) for the PPS-treated group but not for the placebo-treated group. The later held true with $p = 0.01$ to 0.05 for the end of the months 1 and 2 as well.

Table 19 Efficacy data (% of patients improved in terms of pain, urgency) and overall improvement

Parameter	PPS	Placebo	p
Overall improvement three months			
Investigator evaluation	26	11	0.03
Patient self-evaluation			
Overall improved	28	13	0.04
Pain follow-up questionnaire	27	14	0.08
Pain scale	46	29	0.07
Pressure to urinate	22	11	0.08
Urgency scale	39	46	ns
Mean reduction in pain score from baseline	0.5*	0.2	ns
Changes from baseline, voided volume			
Mean volume per void (cc)	9.8	7.6	ns
Increase of ≥20 cc (% pts.)	30	20	ns
Total daily urine volume (cc)	+60	−20	ns

*Significantly different from 0 (p = 0.05).

At the three-month self-evaluation, 22% of the PPS patients and 11% of the placebo patients expressed an improvement in pressure to urinate (**p = 0.08**). This was not confirmed by the urgency scale data which revealed a slight margin of 39% to 46% in favour of placebo.

There was a mean increase in volume per void of 9.8 ml for the PPS-treated patients, and 7.6 ml per void for placebo patients. Among the PPS patients, 30% had an increase of 20ml or more compared with 20% of the placebo patients. The PPS group had a mean increase in total daytime volume of urine at the endpoint of 60 ml compared with a mean decrease of 20 ml for the placebo group. These differences were not statistically significant.

The changes from baseline at the endpoint in the remaining parameters studied were not different between treatments. There were voids per day (-1 for both treatments), percent of patients having 3 less voids per day (32% PPS, 24% placebo), and nocturia (-0.8 PPS, -0.5 placebo).

4) In Parsons et al 1993, based on a previous experience with controlled clinical trials with IC, the voided volume data (which tend to be widely variable between and within patients) were considered to be of secondary importance as a measure of efficacy. A voiding volume profile that measured the time and quantity of all voids during waking hours as well as the number of voids during sleeping hours during 3 consecutive days was completed by the patient before and after 3 months of treatment. This profile provided information concerning changes in average voided volume, frequency and nocturia during the treatment period.

There was a mean increase in volume per void of 20.4 ml for the PPS treated patients and a decrease of 2.1 ml per void for placebo treated patients (not significant). Among the PPS group, 40% had an increase of 20 ml or more compared with 24% of the placebo group (p = 0.02). None of the remaining voiding profile data pertaining to frequency or nocturia revealed any significant differences between the treatment groups.

With respect to improved quality of life, the difference between the treatment groups was not statistically significant for improvement in sleep but approached significance for sexual intercourse (p = 0.06).

Table 20 Efficacy results on secondary endpoints

	PPS	Placebo	P-value

Improved sexual intercourse	31	18	0.06
Mean reduction in pain score from baseline	0.5	0.2	ns
Changes from baseline voided volume			
Mean volume per void (cc)	+20.4	-2.1	ns
Increase of ≥ 20 cc (% pts)	40	24	0.02
Total daily urine volume (cc)	+3	-42	ns

* Primary endpoint: Responder analysis based on a moderate (50%) improvement

5) In Sant et al 2003, Secondary outcome measures included the O'Leary-Sant IC Symptom and Problem Index, the University of Wisconsin Symptom score, patient reported symptoms of pain/discomfort and urgency, and results of a 24-hour voiding diary.

At baseline there was a statistically significant difference (p=0.0037) among groups in voiding frequency with lower frequencies in the combination therapy. No further differences between the groups with regard to baseline characteristics were reported.

Overall, there were no statistically significant differences between the main treatments in symptom changes over time for any of the secondary endpoints.

An overview of the efficacy results generated is presented in the following table.

Table 21 Efficacy results on all endpoints (all patients treated with PPS versus patients not treated with PPS.

	Placebo	PPS
No. randomized	62	59
No. responders (%)*	11 (18)	20 (34)
No. complete secondary end point data (%)**	47 (76)	49 (83)
Mean pain score ± SD (0-9)	-0.7 ± 1.8	-1.2 ± 1.9
Mean urgency score ± SD (0-9)	-0.9 ± 1.6	-1.2±1.6
Mean 24-hr frequency ± SD	-0.9 ± 6.3	-0.7 ± 4.8
Mean IC symptom index ± SD (0-20)	-1.7 ± 3.5	-2.6 ± 3.4
Mean IC problem index ± SD (0-16)	-1.9 ± 2.8	-2.6 ± 3.6
Mean Wisconsin IC score ± SD (0-42)	-6.7 ± 8.2	-6.2 ± 8.9

* Patients who withdrew before 24 weeks were considered non-responder and were included in the denominator for the calculation of response rates in the primary intent to treat analysis

** Results for secondary end points include only those cases with complete data at baseline and 24 weeks, do not represent an intent to treat analysis and should be interpreted cautiously due to the potential bias in withdrawal from study (sample sizes are also slightly less for some secondary end points due to missing values).

6) In Nickel et al 2015, for secondary efficacy evaluations, the patients enrolled in this study rated average pain intensity during the previous 3 days using an 11-point numerical rating scale.

Furthermore, two other Patient-reported outcome questionnaires were used in this study:

- The Patient's Overall Rating of Symptoms Score (PORIS) questionnaire including a total of three questions, one for pain, urgency and overall change. The three questions address the overall change in IC, pain, and urgency after treatment as worse, no better (0% improvement), slightly improved (25%), moderately improved (50%), greatly improved (75%), or symptoms gone (100% improvement).

- The 7-point GRA questionnaire, which was used as the primary endpoint in the study reported by Sant et al., 2003.

Defined secondary efficacy endpoints of the study were:

- A responder analysis based on a 4-point reduction in the ICSI total score

- A responder analysis based on a 50% or greater decrease on the PORIS pain, urgency and overall change in condition scores.

- A responder analysis counting those patients who indicated an at least 6 (moderately improved) or 7 (markedly improved) status on the GRA score.

Moreover, ICSI total score, pain intensity, patient reported response to GRA question 1 and urinary frequency change from baseline were evaluated as secondary endpoints.

There was no statistically significant difference between groups for any secondary endpoints.

An overview of all efficacy results is presented in the following table 25.

Table 22 Efficacy results on all endpoints for the placebo and PPS 300 mg groups.

	Placebo	PPS
No. primary end point 30% or greater ICSI total score decrease (%)	48 (40.7)	52 (42.6)
No. secondary end point responders (%):		
4-Point or greater ICSI total decrease	55 (46.6)	60 (49.2)
50% or Greater PORIS pain improvement	50 (42.4)	51 (41.8)
50% or Greater PORIS urgency improvement	(38.1)	50 (41.0)
50% or Greater PORIS overall condition change improvement	49 (41.5)	50 (41.0)
GRA question 1 moderately/markedly improved	37 (31.4)	44 (36.1)
Other secondary end points:		
No. pts	111	111
Mean ± SD pain intensity score baseline/change	5.2 ± 2.30/ -1.5 ± 2.42	4.6 ± 2.22/ -1.5 ± 2.28
Mean ± SD GRA question 1 score/No. pts	5.1 ± 1.32/90	5.3 ± 1.18/100
No. no efficacy dropouts (%)	7 (5.9)	5 (4.1)
Mean ± SD No. daily urinary frequency baseline/change	16.3 ± 8.10/ -2.7 ± 4.34	14.7 ± 4.08/ -2.6 ± 3.55

The applicant substantiated the efficacy of PPS in applied indication presenting the main results on 6 pivotal studies (see **Table** below).

Table 23 Primary Efficacy results from pivotal studies

Study / IC definition	**Primary effect vs pbo**	**Supportive effects vs pbo**	**Comment**
1. Holm-Bentzen et al., 1987 (European Study) IC: part of **IC/BPS**	Not different from pbo (based on EP: symptom evaluations (pain, frequency, nocturia and dysuria) including total symptom score (pre-defined threshold for clinical Relevance: improvement of at least 1,0)	Increased **median MBC** (260 -> 475 ml vs ~300 -> 290 ml, p<0.05) No difference in other EP (Cystometric first sensation and bladder capacity and Mast Cell Count)	**Predominantly negative study, results might be contaminated by broad IC definition** (interpretation)
2. Parsons and Mulholland, 1987 (US Study) IC Falling within ESSIC classification 2X to 3C	**Pain:** RxA: 44 vs 15%, p=0.02 RxA+B: 45 vs 18%, p=0.02 **Urgency**: RxA: 38 vs 18, **p=0.08** RxA+B: 50 vs 19% p=0.03 **Frequency:** RxA: 65 vs 42%, **p=0.06** RxA+B 63 vs 39%, p=0.005	Statistically significant mean % improvement for all 4 symptoms	Predominantly positive study Response: 50 % improvement per symptom; No overall evaluation; patient flow chart (A vs B vs A+B) is not clear; statistical inconsistency in Rx(A) vs Rx(A+B)

	Nocturia:N/A		
3. Mulholland et al., 1990 (US Study) IC Falling within ESSIC classification 2X to 3C	**Overall PRA**: 28 vs 13%, p=0.04	**Overall IRA**: 26 vs 11%, p=0.03; mean reduction of **pain scale:** 0.5 vs 0.2; p=0.05 **Pain:** 27 vs 14%, p=0.08; **Urgency scale** 39 vs 46, p=n.s; **pressure to urinate** 22 vs 11; p=0.08, **voiding characteristics** (p=n.s.)	PRA based on PRO questionnaire (patients reporting 50% (moderate), 75% (great) 100% (complete cure) improvement overall); Partial support (by IRA and pain scale not by individual symptoms)
4. Parsons et al., 1993 (US Study) IC Falling within ESSIC classification 2X to 3C	**Overall PRA**: 32 vs 16%, p=0.01	**Overall IRA**: 26 vs 15%, p=0.002; **pain sale** 66 vs 51; p=0.04; **Pain:** 38 vs 18%, p=0.005; **Urgency scale** 61vs 43 p=0.01; **pressure to urinate:** 30 vs 18; p=0.04, **voiding characteristics** (mean volume per void +20.4 vs -2.2 ml, p=n.s.; RA for increase of $\geq$20 ml (40 vs 24%, p=0.02)	RA: same as in Mulholand et al., 1990 Partial support (by IRA, pain, pain scale, urgency scale, pressure to urinate, and in increase of voiding $\geq$20 ml but not by other voiding characteristics)
5. Sant et al., 2003 (US Study) IC Falling within ESSIC classification 2 to 3C	**GRA***: 34 vs 18%; p=0.06	Changes in mean pain score, urgency score, frequency and other scores: p=n.s	This is factorial design study; RA based on GRA (patients reporting at least 6/7 (moderately improved) or 7/7 (markedly improved) on 7 point numerical rating scale)
6. Nickel et al., 2015 (Canadian & US Study)	**Primary RA**: 42.6 vs 40.7%; p=n.s	No changes in secondary RA: $\geq$4-point ICSI decrease; $\geq$50% improvement in PORIS subscales (pain, urgency and overal) and GRA question for moderately/markedly	Primary RA based on a 30% reduction in patient-reported **ICSI score; Predominantly negative study, results might be contaminated by broad IC definition**

IC: part of **IC/BPS**		improvement; p=n.s	**(interpretation)**
MBC: maximal bladder capacity; **GRA:** global response assesment; **ICSI:** O'Leary-Sant Interstitial Cystitis Symptoms Index; **IRA:** investigator RA; **N/A:** not available; **n.s.:** not significant; PORIS: Patient's Overall Rating of Improvement of Symptoms; **Pbo:** Placebo; **PRA:** patient RA; **PRO:** patient reported outcome; **RA:** responder analysis (assesment); **Rx:** treatment arm; ***:** PPS=PPS or PPS+Hydroxyzine; Pbo=Pbo or Pbo+Hydroxyzine.			

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for pivotal trials

<table>
<tr><th>Study</th><th>Design, Hypothesis, treatment groups</th><th>Inclusion criteria</th><th>Endpoints and definitions
Primary endpoints</th><th>Descriptive statistics and estimate variability (primary endpoints)</th><th>Descriptive statistics and estimate variability(main secondary endpoints)</th></tr>
<tr>
<td>Holm-Bentzen (1987)</td>
<td>Randomized, Double-blind, Superiority of 200 mg x 2/ day of PPS versus placebo for 4 months

N = 155 patients

<u>Protocol A</u>: 43 patients were randomized

All patients were female and the median age was 63 years (range 34 to 80 years). 39 completed the trial : 19 received PPS, 20 received placebo

<u>Protocol B:</u> 72 patients were randomized</td>
<td>Clinical and/or cystoscopic evidence of painful bladder disease for at least one year.

<u>Protocol A:</u> more than 28 mast cells per mm2 in the detrusor muscle in a bladder biopsy

<u>Protocol B:</u> all patients had mast cell counts less than 28/mm2; 3 or more voidings each night and more than 10 points on a defined symptom score scale evaluating the symptoms pain, frequency, nocturia and dysuria).</td>
<td>Efficacy endpoints at month 4:
- Symptom evaluation (pain, frequency, nocturia and dysuria) including total symptom score (pre-defined threshold for clinical relevance: improvement of at least 1,0)
- Cystometric first sensation and bladder capacity
- Cystoscopic appearance
- Cystoscopic maximal bladder capacity
- Mast Cell Count</td>
<td><u>Protocol A</u>
Number of patient with a reduction of total symptom score :

<table>
<tr><th></th><th>PPS</th><th>Plac</th><th>p-val</th></tr>
<tr><td>Nb pts</td><td>19</td><td>20</td><td></td></tr>
<tr><td>1.0</td><td>6</td><td>4</td><td>0.4<p<0.5</td></tr>
<tr><td>0.75</td><td>8</td><td>4</td><td>0.1<p<0.2</td></tr>
<tr><td>0.5</td><td>9</td><td>5</td><td>0.1<p<0.2</td></tr>
<tr><td>0.25</td><td>11</td><td>9</td><td>0.4<p<0.5</td></tr>
</table>

<u>Protocol B</u>
Number of patient with a reduction of total symptom score :

<table>
<tr><th></th><th>PPS</th><th>Plac</th><th>p-val</th></tr>
<tr><td>Nb pts</td><td>33</td><td>33</td><td></td></tr>
<tr><td>1.0</td><td>9</td><td>7</td><td>0.5<p< 0.6</td></tr>
<tr><td>0.75</td><td>13</td><td>10</td><td>0.7<p< 0.8</td></tr>
<tr><td>0.5</td><td>15</td><td>14</td><td>p = 0.8</td></tr>
<tr><td>0.25</td><td>18</td><td>17</td><td>p =0.8</td></tr>
</table>
</td>
<td><u>For both protocols</u> :
pre-trial and post-trial symptom values
- median symptom scores before and after the trial
. pain NS
. dysuria NS
. frequency NS
. nocturia NS
. the total symptom score : NS

- The symptom of urgency: no effect of PPS was found.
- petechial bleeding : No difference between the groups

- changes in cystoscopic appearance of the bladder :
<u>Protocol A</u>
PPS group pre-trial and post-trial : (p < 0.01)
<u>Protocol B</u>
Placebo group pre-trial and post-trial: (p < 0.01).

- Increase in bladder capacity
<u>Protocol A</u>
PPS (from 260 to 475 ml) vs placebo (p < 0.05). The bladder capacity in the placebo group remained constant.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design, Hypothesis, treatment groups</th><th>Inclusion criteria</th><th>Endpoints and definitions
Primary endpoints</th><th>Descriptive statistics and estimate variability (primary endpoints)</th><th>Descriptive statistics and estimate variability(main secondary endpoints)</th></tr>
<tr><td></td><td>61 women and 5 men were included; the median age was 51 years (range 29 to 78 years)
66 completed the trial, 33 received PPS, 33 received placebo</td><td></td><td></td><td></td><td><u>Protocol B</u> : NS

- First sensation end bladder capacity between the median pre-trial end post-trial values in PPS and placebo groups in both protocols : NS

- Mast cell count :
<u>Protocol A</u>
Decrease pre-trial and post-trial (p<0.01).
It should be noted that this decrease was similar in the PPS (from 42 to 27 mast cells per mm²) and placebo (from 46 to 32 mast cells per mm²) groups</td></tr>
<tr><td>Parsons and Mulholland (1987)</td><td>Randomized, double-blind, superiority of 200 mg 2x/ day of PPS or 100 mg x3/ day of PPS versus placebo for a minimum of 3 months
Crossover design

N = 75 patients were randomized

62 patients completed the study

10% male and 90% female patients.</td><td>At least one year of symptoms (urgency, frequency, nocturia and/or pain), negative urine cultures, and a cystoscopic examination that showed an ulcer or petechial hemorrhage (after bladder distension), biopsy proved inflammation and negative cytology studies</td><td>Patient-Reported improvement for the four distinct subjective symptoms (urgency, frequency, nocturia and pain) separately
50 % improvement per symptom; no overall evaluation at month 3

If the patient responded to treatment A, he returned in 3 more months and if there still a positive response, crossover to treatment B</td><td>Results of four symptoms evaluated separately in patients in arm A (before crossover)
<table><tr><th></th><th>PPS</th><th>Plac</th><th>p-val</th></tr><tr><td>pain</td><td>12/27 (44%)
33.0± 35</td><td>3/20 (15%)
12.2±14.3</td><td>0.02
0.02</td></tr><tr><td>Urgency</td><td>12/32 (38%)
25.4± 26</td><td>5/28 (18%)
11.6±17</td><td>0.08
0.05</td></tr><tr><td>Frequency</td><td>20/31 (65%)
-5.4</td><td>10/24 (42%)
-1.8</td><td>0.06
0.06</td></tr><tr><td>Nocturia</td><td>-2.1 ±2.2</td><td>-0.9 ±0.8</td><td>0.05</td></tr></table>
Results of four symptoms evaluated separately for patients in treatment arm A and B (after cross-over) :</td><td><table><tr><th></th><th>Placebo</th><th>Drug</th></tr><tr><td>No pts</td><td>29</td><td>34</td></tr><tr><td>Av. No. daily voids
Before therapy
After therapy
Net difference
Net impr. (%)</td><td>
20.1 ± 9
20.8 ± 13
-0.7
6 (21)</td><td>
18.9 ± 9
18.3 ± 10
-0.6
13 (38)</td></tr><tr><td>Av. voided vol. (ml)
Before therapy
After therapy
Av. change</td><td>
80.4 ± 42
84.6 ± 53
4.2</td><td>
85.2 ± 46
102.5 ± 57
17.3</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study</th><th>Design, Hypothesis, treatment groups</th><th>Inclusion criteria</th><th>Endpoints and definitions
Primary endpoints</th><th>Descriptive statistics and estimate variability (primary endpoints)</th><th>Descriptive statistics and estimate variability(main secondary endpoints)</th></tr>
<tr><td></td><td>Ulcers were present in 28% of the patients and pain in 75%.</td><td></td><td></td><td>
<table>
<tr><th></th><th>PPS</th><th>Plac</th><th>p-val</th></tr>
<tr><td rowspan="2">Pain impr</td><td>19/42 (45%)</td><td>7/38 (18%)</td><td>0.02</td></tr>
<tr><td>33 ± 35 (%)</td><td>15.8 ± 26 (%)</td><td>0.01</td></tr>
<tr><td rowspan="2">Urgency impr</td><td>21/42 (50%)</td><td>9/48 (19%)</td><td>0.03</td></tr>
<tr><td>27.6± 31 (%)</td><td>14 ± 24 (%)</td><td>0.01</td></tr>
<tr><td rowspan="2">Frequency</td><td>33/52 (63%)</td><td>16/41 (39%)</td><td>0.005</td></tr>
<tr><td>-5.1(%)</td><td>-0.4(%)</td><td>0.002</td></tr>
<tr><td>Nocturia</td><td>-1.5± 2.9(%)</td><td>-0.5± 0.5 (%)</td><td>0.04</td></tr>
</table>
</td><td></td></tr>
<tr><td>Mulholland (1990)</td><td>Randomized, double-blind, superiority of 100 mg of PPS versus placebo

N = 110 patients
54 patients received PPS
56 patients received placebo

N = 98 patients
Completed the 3 month study
51 patients received PPS, 47 patients received placebo
Mean age 43.3 years
91% females</td><td>Urgency expressed as “moderate” on a 5 point analog scale, Frequency of at least 10 voids per day Nocturia of at least 2 voids per night, Pain as recorded on a 5-point analog scale, Continous duration of symptoms of at least one year, Failed previous conventional therapy such as chlorpactin, hydrodilatation, or DMSO, Average voided volume of 200 ml or less measured over a three day period,</td><td>Patient Reported Outcome questionnaire based on six point scale global response assessment (GRA) (patients reporting 50% (moderate), 75% (great) 100% (complete cure) improvement overall) at month 3</td><td>Overall improvement at M3 :
. <u>Patient self-evaluation</u>
- PPS : 28%
- Placebo : 13%
p-value : 0.04

. <u>Investigator evaluation</u>
- PPS : 26%
- Placebo : 11%
p-value : 0.03</td><td>
<table>
<tr><th></th><th>PPS</th><th>Plac</th><th>p-val</th></tr>
<tr><td>Pain (quest)</td><td>27</td><td>14</td><td>0.08</td></tr>
<tr><td>Pain (scale)</td><td>46</td><td>29</td><td>0.07</td></tr>
<tr><td>Pressure to urinate</td><td>22</td><td>11</td><td>0.08</td></tr>
<tr><td>Urgency scale</td><td>39</td><td>46</td><td>ns</td></tr>
<tr><td>Mean red. In pain score from baseline</td><td>0.5</td><td>0.2</td><td>NS</td></tr>
<tr><td>Mean vol per void from baseline</td><td>9.8</td><td>7.6</td><td>NS</td></tr>
<tr><td>Incr of ≥ 20 cc (% pts) from baseline</td><td>30</td><td>20</td><td>NS</td></tr>
<tr><td>Total</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design, Hypothesis, treatment groups</th><th>Inclusion criteria</th><th>Endpoints and definitions
Primary endpoints</th><th>Descriptive statistics and estimate variability (primary endpoints)</th><th>Descriptive statistics and estimate variability(main secondary endpoints)</th></tr>
<tr><td></td><td>100% white race
Placebo:
Mean age 45.3 years
87% females
95% white race</td><td>Negative urine culture and cytology
Cystoscopic examination under anaesthesia (80 cm of water and 1 minute distention) showing petechial hemorrhages or ulcers with gross blood in the fluid return and a bladder capacity of 800 ml or less.</td><td></td><td></td><td>
<table>
<tr><td>daily urine vol (cc)</td><td>+60</td><td>-20</td><td>NS</td></tr>
<tr><td>Voids per day</td><td>-1</td><td>-1</td><td>NS</td></tr>
<tr><td>3 voids less per day (% pts)</td><td>32</td><td>24</td><td>NS</td></tr>
<tr><td>Nocturia</td><td>-0.8</td><td>-0.5</td><td>NS</td></tr>
</table>

It should be noted that the mean reduction in pain from baseline as measured by the pain scale was significantly different from zero (p = 0.05) for the PPS-treated group but not for the placebo-treated group. The latter held true with
p = 0.01 to 0.05 for the end of months 1 and 2 as well.</td></tr>
<tr><td>Parsons (1993)</td><td>Randomized, double-blind, superiority of 100 mgx3/day of PPS versus placebo for 3 months

N = 148 patients were enrolled, 74 in each treatment group

130 patients completed the</td><td>Anaesthetic bladder capacity (350 – 1,000 cc), Number of voids per day (more than 8) Average voided volume (50 to 200 cc), Nocturia (at least 1 or 2), Patients lacking 1 or 2 of these criteria were entered into the study but they had to have pain and/or moderate urgency, negative</td><td>Patient Reported Outcome questionnaire based on six point scale global response assessment (GRA) (patients reporting 50% (moderate), 75% (great) 100% (complete cure) improvement overall) at month 3</td><td>Overall improvement at M3 :

. <u>Patient self-evaluation</u>
- PPS : 32%
- Placebo : 16%
p-value : 0.01

. <u>Investigator assessment</u>
- PPS : 36%
- Placebo : 15%
p-value : 0.002</td><td>
<table>
<tr><td></td><td>PPS</td><td>Plac</td><td>p-val</td></tr>
<tr><td>Pain (quest)</td><td>38</td><td>18</td><td>0.005</td></tr>
<tr><td>Pain (scale)</td><td>66</td><td>51</td><td>0.04</td></tr>
<tr><td>Pressure to urinate</td><td>30</td><td>18</td><td>0.04</td></tr>
<tr><td>Urgency scale</td><td>61</td><td>43</td><td>0.01</td></tr>
<tr><td>Impr Sexual Inter course</td><td>31</td><td>18</td><td>0.06</td></tr>
<tr><td>Mean red. In pain score</td><td>0.5</td><td>0.2</td><td>NS</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design, Hypothesis, treatment groups</th><th>Inclusion criteria</th><th>Endpoints and definitions
Primary endpoints</th><th>Descriptive statistics and estimate variability (primary endpoints)</th><th>Descriptive statistics and estimate variability(main secondary endpoints)</th></tr>
<tr>
<td></td>
<td>study 65/ arm
Mean age 42.7 years
100% females
97% white
Placebo:
Mean age 45.5 years
93% females
96% white</td>
<td>urine cytology studies and cultures, and cystoscopic findings of petechial haemorrhages and blood in the fluid return after bladder dilation.</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>from baseline</td><td></td><td></td><td></td></tr>
<tr><td>Mean vol per void from baseline</td><td>+20.4</td><td>-2.1</td><td>NS</td></tr>
<tr><td>Incr of ≥ 20 cc (% pts) from baseline</td><td>40</td><td>24</td><td>0.02</td></tr>
<tr><td>Total daily urine vol (cc)</td><td>+3</td><td>-42</td><td>NS</td></tr>
</table>
</td>
</tr>
<tr>
<td>Sant (2003)</td>
<td>Randomized double-blind, superiority of 100 mg 3x/day of PPS versus placebo or 50 mg of hydroxyzine/ day or combination 50 mg/day of hydroxyzine + 100 mg 3x/day of PPS versus placebo or hydroxyzine alone or PPS alone for 6 months

2x2 factorial design
N = 121 patients randomized

96 patients</td>
<td>At least 18 years
Diagnosis of IC, confirmed by cystoscopy and hydrodistention, following NIDDK criteria (National Institutes for Diabetes and Digestive and Kidney Diseases)
Moderate symptoms of urinary frequency (at least 11 times daily) and pain/discomfort (at least 4 on a 0 to 9 Likert scale) for at least 24 weeks</td>
<td>Patient-reported 7-point centred global response assessment (GRA) score as primary efficacy evaluation (patients reporting at least 6 moderately improved or 7 markedly improved on 7 point numerical rating scale)</td>
<td>Symptom score at week 24

<table>
<tr><th></th><th>Plac</th><th>Hydro</th><th>PPS</th><th>Combination</th></tr>
<tr><td>Randomized</td><td>31</td><td>31</td><td>29</td><td>30</td></tr>
<tr><td>Responders</td><td>4 (13)</td><td>7 (23)</td><td>8 (28)</td><td>12 (40)</td></tr>
</table>

- PPS: 20/59 (34%)
. PPS alone: 8/29 (28%)
. PPS + hydroxyzine: 12/30 (40%)
- Non-PPS: 11/62 (18%)
. Hydroxyzine alone : 7/31 (23%)
. Placebo : 4/31 (13%)
→ PPS vs non PPS :
p-value : 0.064 (NS)

- Hydroxyzine: 19/61 (31%)</td>
<td>
<table>
<tr><th></th><th>PPS</th><th>Placebo (non – PPS)</th></tr>
<tr><td>Complete secondary Endpoint data (%)</td><td>49 (83%)</td><td>47 (76%)</td></tr>
<tr><td>Mean pain score ± SD (0-9)</td><td>-1.2 ± 1.9</td><td>-0.7 ± 1.8</td></tr>
<tr><td>Mean urgency score ± SD (0-9)</td><td>-1.2 ± 1.6</td><td>-0.9 ± 1.6</td></tr>
<tr><td>Mean 24h frequency</td><td>-0.7 ± 4.8</td><td>-0.9 ± 6.3</td></tr>
<tr><td>Mean IC symptom index ± SD (0-20)</td><td>-2.6 ± 3.4</td><td>-1.7 ± 3.5</td></tr>
<tr><td>Mean IC problem index ± SD (0-16)</td><td>-2.6 ± 3.6</td><td>-1.9 ± 2.8</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design, Hypothesis, treatment groups</th><th>Inclusion criteria</th><th>Endpoints and definitions
Primary endpoints</th><th>Descriptive statistics and estimate variability (primary endpoints)</th><th>Descriptive statistics and estimate variability(main secondary endpoints)</th></tr>
<tr>
<td></td>
<td>provided complete follow-up data.

89% females
84% white
Median age 45 years</td>
<td></td>
<td></td>
<td>. hydroxyzine alone: 7/31 (23%)
. hydroxyzine + PPS : 12/30 (40%)
- Non-hydroxyzine : 12/60 (20%)
. Placebo: 4/31 (13%)
. PPS alone: 8/29 (28%)
→ Hydroxyzine vs non-hydroxyzine : p-value : 0.26 (NS)</td>
<td>
<table>
<tr><td>Mean Wisconsin IC score ± SD (0-42)</td><td>-6.2 ± 8.9</td><td>-6.7 ± 8.2</td></tr>
</table>
There was a trend for a higher response rate in the PPS treatment arm at week 24
<table>
<tr><th></th><th>Plac</th><th>Hydro</th><th>PPS</th><th>Combination</th></tr>
<tr><td>Complete secondary Endpoint data (%)</td><td>23/74)</td><td>24 (77)</td><td>26 (90)</td><td>23 (77)</td></tr>
<tr><td>Mean pain score ± SD (0-9)</td><td>-1.0 ± 1.8</td><td>-0.5 ± 1.8</td><td>-0.8 ± 1.8</td><td>-1.6 ± 1.9</td></tr>
<tr><td>Mean urgency score ± SD (0-9)</td><td>-1.1 ± 1.7</td><td>-0.8 ± 1.6</td><td>-1.0 ± 1.6</td><td>-1.3 ±1.6</td></tr>
<tr><td>Mean 24-hr frequency ± SD</td><td>-0.5 ± 5.3</td><td>-1.2 ± 7.3</td><td>-0.2 ± 5.0</td><td>-1.4 ± 4.4</td></tr>
<tr><td>Mean IC symptom index ± SD (0-20)</td><td>-2.3 ± 3.4</td><td>-1.3 ± 3.6</td><td>-1.7 ± 3.0</td><td>-3.6 ± 3.6</td></tr>
<tr><td>Mean IC problem index</td><td>-2.3 ± 3.1</td><td>-1.5 ± 2.6</td><td>-1.9 ± 3.3</td><td>-3.4 ± 3.6</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design, Hypothesis, treatment groups</th><th>Inclusion criteria</th><th>Endpoints and definitions
Primary endpoints</th><th>Descriptive statistics and estimate variability (primary endpoints)</th><th>Descriptive statistics and estimate variability(main secondary endpoints)</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>± SD (0-16)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean Wisconsin IC score ± SD (0-42)</td><td>-7.2 ± 9.1</td><td>-7.2 ± 9.1</td><td>-5.0 ± 9.5</td><td>-7.5 ± 8.2</td></tr>
</table>
</td></tr>
<tr><td>Nickel (2015)</td><td>Randomized double-blind, superiority of 100 mg 3x/ day of PPS versus placebo for 24 weeks

N = 369 eligible patients
. placebo : n= 118
. PPS 100 mg/day : n = 129
. PPS 300 mg/day : n = 122

206 patients completed the 24 weeks study
. placebo : n = 63
. PPS 100 m/day : n = 74</td><td>Total score of 8 or greater on ICSI and a score of greater than 0 on each component item (bladder pain, urinary urgency, frequency and nocturia). At least 10 voids per day of which 1 or more were during the night. No intravesical therapy (bladder distension or DMSO) during the 4 weeks before screening. No evidence of microscopic haematuria or evaluation positive for significant urological disease</td><td>A responder analysis based on a 30% improvement in the Interstitial Cystitis Symptom Index (ICSI)</td><td>30% or greater ICSI total score decrease (%) : primary endpoint

. PPS 100 mg/day : 51/128 (39.8%)
. PPS 100 mg 3x/day: 52/122 (42.6%)
. Placebo: 48/118 (40.7%)
P- value : NS

Post-hoc analysis :
n = 94 patients with NIDDK criteria
. Placebo: 16/32 (50%)
. PPS 100 mg/day: 10/33 (30.3%)
. PPS 100 mg 3x/day: 10/29 (34.5%)
P-value : NS</td><td>Secondary endpoints responders (%)
<table>
<tr><th></th><th>PPS 300 mg</th><th>Placebo</th></tr>
<tr><td>. 4-point or greater ICSI total decrease</td><td>60 (49.2%)</td><td>55 (46.6%)</td></tr>
<tr><td>. 50 % or greater PORIS pain impr</td><td>51 (41.8%)</td><td>50 (42.4%)</td></tr>
<tr><td>. 50% or greater PORIS urgency impr</td><td>50 (41%)</td><td>38.1%</td></tr>
<tr><td>. 50% or greater PORIS overall condition change GRA question 1 moderately /markedly</td><td>44 (36.1%)</td><td>37 (31.4%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design, Hypothesis, treatment groups</th><th>Inclusion criteria</th><th>Endpoints and definitions
Primary endpoints</th><th>Descriptive statistics and estimate variability (primary endpoints)</th><th>Descriptive statistics and estimate variability(main secondary endpoints)</th></tr>
<tr><td></td><td>. PPS 300 mg/day : n = 69
Men and women of at least 18 years</td><td>within the prior year. No treatment with drugs known to affect IC/BPS symptoms (i.e. antidepressants, antihistamines, antispasmodics or anticholinergics) within the 4 weeks before screening.</td><td></td><td></td><td>
<table>
<tr><td>improved</td><td></td><td></td></tr>
</table>
Other secondary endpoints
<table>
<tr><th></th><th>PPS 300 mg</th><th>Placebo</th></tr>
<tr><td>Nb pts</td><td>111</td><td>111</td></tr>
<tr><td>Mean ± SD pain intensity score baseline/ change</td><td>4.6 ± 2.22/ -1.5 ± 2.28</td><td>5.2 ± 2.30/ -1.5 ± 2.42</td></tr>
<tr><td>Mean ± SD GRA question 1 score/ nb pts</td><td>5.3 ±1.18/100</td><td>5.1 ± 1.32/ 90</td></tr>
<tr><td>No efficacy dropouts</td><td>5 (4.1%)</td><td>7 (5.9%)</td></tr>
<tr><td>Mean ± SD nb daily urinary frequency baseline/ change</td><td>14.7 ± 4.08/ -2.6 ± 3.55</td><td>16.3 ± 8.10/ -2.7 ± 4.34</td></tr>
</table>
</td></tr>
</table>

Analysis performed across trials (pooled analyses and meta-analysis)

Primary meta-analysis conducted by the applicant

The objective of this meta-analysis was to evaluate the efficacy of PPS for the treatment of interstitial cystitis (IC) versus placebo by combining the results of available placebo controlled studies.

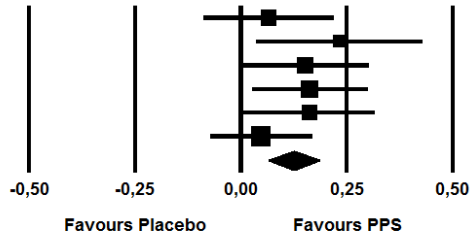
Overall, based on the Applicant, all six studies were sufficient comparable to be included into the meta-analysis. This decision corresponded to the proceeding by Hwang et al., 1997 who included the four studies which were available at that time and to the proceeding by Dimitrakov et al., 2007 who included all five of the six studies available at that time. As the latest clinical study was just recently published by Nickel et al., 2015, none of the two published meta-analyses included this large clinical study.

The meta-analysis included all 6 pivotal studies performed between 1987 and 2015, of which 5 of them were carried out between 1987 and 2003. They were relatively small trials, mainly exploratory, except the Nickel study which was a true confirmatory trial with a large sample size (targeted 645 subjects, actual 368 and 240 retained in the meta-analysis). The primary endpoint of the meta-analysis was the responder rate based upon a patient's global response assessment (GRA), as defined in the individual studies when available or calculated afterwards if not directly available in studies. The main analysis was performed on the ITT population (all randomized subjects in trials) along with several sensitivity analysis, in order to test the robustness of the main results.

Sensitivity analyses consisted in primary (GRA) and secondary endpoints (pain and urgency) analysis carried out in populations with different size: "ITT population" and "As-reported population" (subjects taken into account in publications), including all studies or only part of them.

Table 24 Primary meta-analysis, ITT, global response assessment

Study name	Outcome	Benefit difference	Standard error	Lower limit	Upper limit	p-Value
Holm-Bentzen 87	Overall 4 steps	0,066	0,078	-0,087	0,218	0,398
Parsons 87	Overall Impr Self	0,233	0,100	0,037	0,428	0,020
Mulholland 90	Overall Impr Self	0,153	0,075	0,005	0,300	0,042
Parsons 93	Overall Impr Self	0,162	0,069	0,026	0,298	0,019
Sant 2003	Overall GRA	0,162	0,078	0,008	0,315	0,039
Nickel 2015	Overall GRA	0,047	0,061	-0,072	0,167	0,440
		0,124	0,030	0,064	0,183	0,000



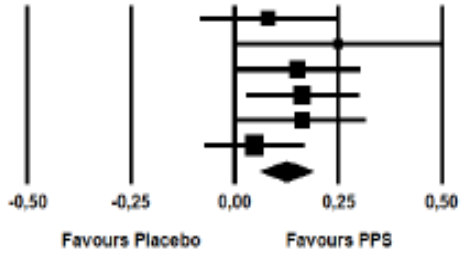
Patients as randomized; missing results considered as failures

There is no indication of heterogeneity in standard measures:

Q-value = 4.019 < 5 (=expected value under homogeneity), p=0.547, I^2=0. Despite I^2=0, the results of the Nickel and Holm-Bentzen studies may deviate in reality to some degree from the other studies, but this is not discovered because of the high homogeneity of the results of the other 4 studies.

Table 25 Primary meta-analysis, as reported, global response assessment

Study name	Outcome	Benefit difference	Standard error	Lower limit	Upper limit	p-Value
Holm-Bentzen 87	Overall 4 steps	0,081	0,084	-0,084	0,245	0,335
Parsons 87	Overall Impr Self	0,250	0,127	0,001	0,499	0,049
Mulholland 90	Overall Impr Self	0,153	0,075	0,005	0,300	0,042
Parsons 93	Overall Impr Self	0,162	0,069	0,026	0,298	0,019
Sant 2003	Overall GRA	0,162	0,078	0,008	0,315	0,039
Nickel 2015	Overall GRA	0,047	0,061	-0,072	0,167	0,440
		0,124	0,031	0,063	0,185	0,000



Patients as reported

There is no indication of heterogeneity in standard measures: Q-value = 3.518, p=0.621, I^2=0. Benefit difference is defined as the estimated difference in responder rates of treatment groups PPS minus placebo within each study and overall.

Different results between the two approaches, ITT and as reported in the publication exist in the two studies from 1987 only, because the other 4 studies were already reported according to the ITT principle in their study publications.

Despite the heterogeneous results of the six studies, the estimated benefit differences in overall improvement are **12.4%** both for the ITT approach and the as reported approach; the related p-values are **p<0.001**. The lower limits of the 95%- confidence intervals are **6.4% and 6.3%** and thus both are > 5.0% indicating a relevant superiority over placebo.

Co-primary meta-analysis conducted by the applicant

In order to reflect the prioritisation of efficacy endpoints as intended by the sponsors of the pivotal studies, the applicant also conducted a co-primary meta-analysis, evaluating the responder rates based on the pre-defined primary endpoints per study.

The co-primary meta-analysis based on the ITT population estimated a difference in the responder rates of **11.9%** (p<0.001) (95% IC: 5.8%-18%) between PPS and placebo-treatment. A very small, non-significant heterogeneity was detected between the studies (Q=5.098, p=0.404, I^2=1.92%).

When evaluating the “as reported” results instead of the results in the ITT population in the co-primary meta-analysis, the difference in responder rates was practically equal (**11.9%**) (p<0.001) without any indication of heterogeneity (Q=4.600, p=0.467, I^2=0).

Sensitivity-analysis conducted by the applicant

Beyond the main meta-analyses (primary and co-primary), two additional groups of comparative meta-analyses were designed and conducted based on the following endpoints:

- Response in individual symptoms,

- Mean change in individual and overall symptom scores.

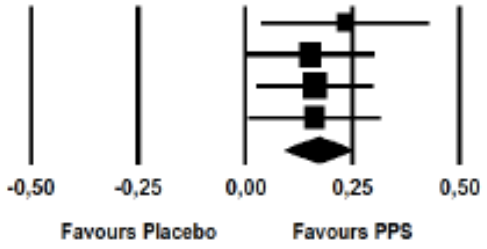
The patients in the studies reported by Parsons and Mulholland, 1987; Mulholland et al., 1990; Parsons et al., 1993 and Sant et al., 2003 all fulfilled the NIDDK criteria for Interstitial Cystitis and met the ESSIC categories 2X or 3C. Accordingly, the patient population in those studies represent a more homogeneous group than the patients enrolled by Holm-Bentzen et al., 1987 and Nickel et al, 2015.

Therefore, a sensitivity analysis was conducted including only the 4 studies enrolling this more homogeneous patient population expecting a more precise estimation of the treatment effect.

The higher degree of homogeneity of this sensitivity meta-analysis is reflected by a very small Q value of Q=0.470 far away from its expected value of 4-1 = 3. The effect size for this homogeneous patient population was greater than the effect size seen in the primary and co-primary meta-analysis and showed a statistically significant difference of PPS over placebo (p<0.001) with an estimated difference in responder rates of **17.0% with a 95% IC of [9.3%- 24.7%].**

Table 26 Sensitivity analysis, ITT, Global response assessment

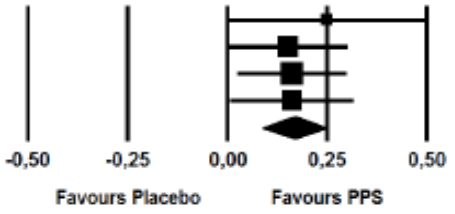
Study name	Outcome	Benefit difference	Standard error	Lower limit	Upper limit	p-Value
Parsons 87	Overall Impr Self	0,233	0,100	0,037	0,428	0,020
Mulholland 90	Overall Impr Self	0,153	0,075	0,005	0,300	0,042
Parsons 93	Overall Impr Self	0,162	0,069	0,026	0,298	0,019
Sant 2003	Overall GRA	0,162	0,078	0,008	0,315	0,039
		0,170	0,039	0,093	0,247	0,000



Patient numbers as randomized

Table 27 Sensitivity analysis, as reported, Global response assessment

Study name	Outcome	Benefit difference	Standard error	Lower limit	Upper limit	p-Value
Parsons 87	Overall Impr Self	0,250	0,127	0,001	0,499	0,049
Mulholland 90	Overall Impr Self	0,153	0,075	0,005	0,300	0,042
Parsons 93	Overall Impr Self	0,162	0,069	0,026	0,298	0,019
Sant 2003	Overall GRA	0,162	0,078	0,008	0,315	0,039
		0,168	0,041	0,089	0,248	0,000



Patient numbers as reported

As in the ITT analysis above and as expected, there is no indication of heterogeneity between the study results: Q = 0.471, p = 0.925, I^2 = 0.

The estimated combined benefit difference is **16.8%** with a 95%-confidence interval of [**8.9%,** 24.8%].

As the primary efficacy endpoints in the four studies included in the sensitivity analysis are patient-reported global response assessments, the sensitivity analysis applies for the primary as well as for the co-primary meta-analysis.

The Applicant provided an additional meta-analysis to support the efficacy of PPS in IC.

To support the clinical relevance of the benefit differences calculated in the pivotal studies, the Applicant provided a further meta-analysis combining the responder rates of the different endpoints separately. In this meta-analysis, only GRA, pain and urgency evaluation were performed. The results of this meta-analysis are provided below separately for all six pivotal studies and for the four pivotal studies which used a traditional diagnostic approach.

For all six pivotal studies, the results for PPS are around **33%** and **20%** for placebo with an overlap in IC 95% for pain.

In the meta-analysis including only the 4 pivotal studies with traditional diagnostic approach, the results for PPS are around **31%** and **15 %** for placebo with no overlap in IC 95%. Based on the Applicant, the high placebo response rates of **15-20%** were expected in a disease like IC as condition like depression, functional disorders and pain are known to be associated with high placebo-rates in randomized, double-blind, placebo-controlled studies.

Table 28 Responder rates per treatment arm (six pivotal studies)

	PPS (95% CI)	Placebo (95% CI)
GRA	33,0% (28.6% - 37.7%)	19.3% (13.9% - 26.3%)
Pain	36.7% (31.4% - 42.3%)	21.4% (11.6% - 36.2%)
Urgency	31.3% (23.0% - 41.0%)	18.4% (8.6% - 35.3%)

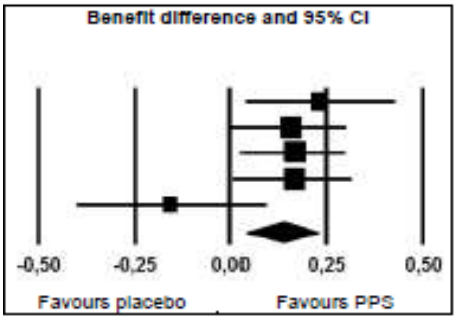
Table 29 Responder rates per treatment arm (four pivotal studies)

	PPS (95% CI)	Placebo (95% CI)
GRA	33.0% (27.1% - 39.4%)	15.8% (11.6% - 21.2%)
Pain	32.7% (26.0% - 40.3%)	14.2% (9.6% - 20.6%)
Urgency	27.4% (21.1% - 34.8%)	14.2% (9.6% - 20.6%)

The applicant provided a further meta-analysis which took into consideration the results of the post Hoc analysis of Nickel et al study in the subgroup of patients with IC (2X to 3C according to the ESSIC classification). Compared to the sensitivity analysis including only the four pivotal studies, which included the pre-defined homogeneous patient population of patients falling within ESSIC classification 2X to 3C, the estimated benefit difference in success rates has decreased from **17.0% to 13.3% where this smaller difference is still statistically significant (p=0.007)**.

Table 30 Meta-analysis: incl Nickel et al subgroup ITT. Global response assessment (ICSI for Nickel et al 2015)

		PPS-group			Placebo-group			Statistics				
			Responders			Responders		Benefit	Standard	Lower	Upper	p-value
Study Name	Outcome	N	(n)	(%)	N	(n)	(%)	difference	error	limit	limit	
Parsons 87	Overall GRA	38	15	39,5	37	6	16,2	0.233	0.100	0.037	0.428	0.020
Mulholland 90	Overall GRA	54	15	27,8	56	7	12,5	0.153	0.075	0.005	0.300	0.042
Parsons 93	Overall GRA	74	24	32,4	74	12	16,2	0.162	0.069	0.026	0.298	0.019
Sant 03	Overall GRA	59	20	33,9	62	11	17,7	0.162	0.078	0.008	0.315	0.039
Nickel 15 (Subgroup)	ICSI 30%	29	10	34.5	32	16	50.0	-0,155	0.125	-0.400	0.090	0.214
								0.133	0.050	0.036	0.230	0.007



Supportive meta-analysis conducted by the applicant evaluating the main symptoms of IC

In order to provide more objective information on the efficacy of PPS, the pivotal clinical studies were also evaluated with regard to the information provided on the main symptoms pain and urgency.

Effects on symptom scores for pain and urgency are reported in the publications from Parsons and Mulholland, 1987; Mulholland et al., 1990; Parsons et al., 1993 and Nickel et al., 2015. The publication from Holm-Bentzen et al., 1987 reported effects on pain, but not on urgency. The publication from Sant et al., 2003 reported no responder rates on different symptoms, but just overall scores and their mean changes from baseline.

The supportive meta-analyses mainly used the reported effect size on the symptoms pain and urgency and calculated the effects sizes on the ITT population as main outcome.

The Holm-Bentzen et al., 1987 study could not be included in the meta-analysis because there are no response data available for Urgency but there are good data for Frequency. Therefore, this study was excluded in meta-analysis of symptom urgency. Likewise, the study of Sant at 2003 was excluded, as rates of improvement in urgency were not available for this study. However, meta-analysis were performed in including available data of frequency instead of urgency for the Holm-Bentzen et al 1987 study and urgency success rates for the Sant et al 2003 from the overall improvement result of the study with a method of data extraction.

Statistically significant benefit differences of 12.1% (ITT approach, Sant et al 2003 excluded) (IC 95% [0.03-0.211], p =0.009) and 9.9% (ITT approach, Holm-Bentzen et al 1987 and Sant et al excluded 2003) (IC 95% [0.029-0.168], p = 0.005) were reached for an improvement of pain and urgency evaluated respectively in the supportive meta-analyses.

Imputation of results for the studies Sant et al., 2003 and Holm-Bentzen et al., 1987 lead to a benefit difference of 12.3% for the ITT (IC 95% [0.049-0.198], p = 0.001]) and “as reported” (IC 95% [0.044-0.203], p = 0.002]) approach for pain and 10.3% (ITT approach)(IC 95%[0.044-0.162], p = 0.001) or 10.3% (as reported approach) (IC 95% [0.04-0.0165], p = 0.001) for urgency.

The sensitivity analyses including only the four studies (without Holm-Bentzen et al 1987 and Nickel et al 2015) with a better defined patient population revealed a benefit difference of 17.6% for pain (IC 95% [0.1-0.251], p = 0) and 13.0% for urgency (IC 95% [0.057-0.202], p = 0).

Supportive studies

Nine supportive studies were provided by the applicant, most of them were open-label and uncontrolled or retrospective studies with a small number of patients and published between 1983 and 2000. Only 4 were more recent and published from 2005 and 2008.

Among these 9 studies, 2 long-term studies “**Hanno et al 1997**”study in 2809 patients from 1986 to 1996 and “**Jepsen et al 1998**” study in 97 patients from 1987 to 1995, showed that improvement increased with duration of treatment in patients treated with PPS (100 mgX3/ day). However, it should be noted that PPS could be curative for some patients and that patients receiving treatment for a duration > 90 months showed no further improvement or worsening in symptom values (“tachyphylaxis”).

One randomized, double-blind dose-ranging study was performed by **Nickel et al 2005** to evaluate three different doses of PPS (100 mg x3/ day, 200 mg x3/ day, 300 mg x3/day) for 32 weeks in 380 patients. No statistical difference was found among the 3 doses regarding ICSI scores and PORIS scores. Therefore, response to treatment was not dose-dependent. However, when patients were categorized by the severity of their symptoms at baseline according to the ICSI, the response in those with mild and moderate symptoms were not dose dependent but in patients with severe symptoms at baseline, a better response to the 600 mg dose was observed (p = 0.028).

Another randomized double-blind clinical trial was performed by **Davis et al 2008** to evaluate the safety and efficacy of intravesical PPS administration on top of oral PPS treatment in 41 women. The use of the association of intravesical PPS and oral PPS appears to enhance the proliferation of the GAG layer of the bladder, to produce greater relief and return to normal protective coating when maintained with oral PPS.

An open-label study was performed to evaluate the safety and efficacy of subcutaneous low dose heparin application on top of oral PPS application in 41 patients (**Van Ophoven et al 2005**). The results show that the subgroup of patients with initially less favourable PPS treatment outcome (minor group) predominantly benefited from additional administration of subcutaneous heparin due mainly to the significant reduction of pain intensity.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

All the six pivotal studies were placebo controlled double-blind, multicentre studies, of which the objectives were to assess the superiority of PPS versus placebo (except Sant et al 2003 which evaluated the superiority of PPS versus placebo and hydroxyzine). All but one of 6 pivotal studies

conducted more than 10 years ago (except and Nickel et al. (2015) study) were small studies and used old methodological standard. The Nickel study was a true confirmatory trial with a large sample size (targeted 645 subjects, actual 368 and 240 retained in the meta-analysis).

The conduct of the pivotal studies met recruitment difficulties especially in the more recent studies (Sant et al 2003 and Nickel et al 2015). Indeed, these latter studies were performed in USA and Canada when PPS was already commercially available which lead to recruitment of non-naïve PPS patients or patients with a less severe disease (milder symptoms) than in the 4 earlier studies. In the Nickel et al study, there were no cut-off criteria for pain or urgency, no determination of flare status, no entry criterion based on cystoscopy findings and no exclusion for commonly associated conditions such as irritable bowel disease, depression or pelvic floor dysfunction disease. Moreover, this study was stopped for futility as continuing the study until its planned sample size would not have significantly increased the chance of a successful trial.

On the other hand it seems that the 3 earlier studies (Parsons and Mulholland 1987, Mulholland et al 1990 and Parsons et al 1993) were recruiting (a) without clear hypothesis tested and (b) without clear management of selection biases as these studies were performed with old methodological requirements.

Sample sizes to test certain hypothesis were calculated only for three of the six pivotal studies: in Holm-Bentzen et al 1987 study (40 patients per group), Sant et al 2003 study (136 patients per group), and Nickel et al 2015 study (target 645 patients would yield 600 (200 per treatment arm). No sample sizes were defined prospectively for Parsons and Mulholland 1987 study, Mulholland et al 1990 study, and Parsons et al 1993 study. This is a weakness of this literature based application.

The population included in the pivotal studies differs between the studies. The population was included with different IC definitions, mixing both broad IC/BPS (i.e. In European Holm-Bentzen et al. 1987 Study and in Canadian/US Nickel et al 2015 Study) definitions meeting the ESSIC classification 2X and 3C (i.e. in US Parsons and Mulholland 1987 Study, Mulholland et al 1990 Study, Parsons et al 1993 Study, and in Sant et al 2003 Study) but it is agreed that the broader population (IC/BPS) includes IC (2X to 3C) disease as BPS is a very broad symptom complex including also patient with milder severity than IC. “Pain” was considered as the key main symptom of the interstitial cystitis.

Considering the fact that no outcome measure is currently standardized the patient’s global assessment or any impact of the IC disease are considered as the most relevant outcome measures. According to the guidelines on chronic pelvic pain (Engeler 2015), symptom scores, evaluated with the O’Leary-Sant Symptom Index also known as the Interstitial Cystitis Symptom Index (ICSI), may help to assess the patient and act as outcome measures. However, this is a subjective assessment, other more objective criteria could have been taken into consideration such as increase of working or waking hours, return to work or school or increase of physical or sexual activities.

Given the heterogeneous population of the six pivotal studies, the applicant proposed to restrict the indication to patients diagnosed with IC using the traditional approach including cystoscopy with or without hydrodistension corresponding to the IC criteria established by the National Institute of diabetes and digestive and kidney diseases (NIDDK) (Cases meeting the ESSIC classification 2X and 3C would meet the NIDDK criteria for IC). These IC patients were included in four pivotal studies (Parsons and Mulholland 1987, Mulholland et al 1990, Parsons et al 1993 and Sant et al 2003), of whom 3 met the primary endpoints (Parsons and Mulholland 1987, Mulholland et al 1990, Parsons et al 1993).

Indeed, several associations such as International Society for the Study of bladder painful symptom (ESSIC), American urology association (AUA), and European association of Urology (EAU) recommend

to use preferentially “bladder pain syndrome” or “painful bladder syndrome” (PBS) instead of interstitial cystitis (IC). Therefore the CHMP considered that the indication should refer to BPS with glomerulations / Hunner’s lesions to outline the population in which efficacy was significantly demonstrated in the pivotal trials (formerly described as IC).

Regarding the study outcomes/endpoints, the key study endpoints/outcomes in all 6 pivotal studies were patient-reported outcomes via patient responder analysis. This might be considered as a reasonable approach for this type of disease. The responder definitions based on 6-point or 7-point GRA assessment used for primary efficacy evaluation in three pivotal studies are quite identical (Mulholland et al., 1990; Parsons et al., 1993, Sant et al., 2003) and the responder definition based on ICSI scores used for primary efficacy evaluation in the latest study (Nickel et al., 2015) was shown to correlate with the GRA-responders. Although no global response assessment was conducted in the study reported by Parsons and Mulholland, 1987, the data imputation used for the meta-analysis conducted by the applicant is deemed sufficiently comparable. For the responder analysis used in the study reported by Holm-Bentzen et al, 1987 comparability with the other responder definitions could not be demonstrated.

If only the four pivotal studies are considered which enrolled a homogeneous and clear defined patient population representative for the targeted patient population (Parsons and Mulholland, 1987, Mulholland et al., 1990; Parsons et al., 1993, Sant et al., 2003), the responder analysis are deemed comparable.

Efficacy data and additional analyses

- **Results on primary endpoints**

The six pivotal randomised, double-blind, placebo-controlled studies were identified as pivotal database to evaluate the efficacy and safety of PPS. Only 3 of them met the primary endpoints “overall global improvement” (assessed by a self-evaluation confirmed by an investigator’s evaluation) in comparison to placebo (Parsons and Mulholland, 1987; Mulholland et al., 1990; Parsons et al., 1993).

Indeed, the first study (Holm-Bentzen 1987) failed to detect a statistically significant difference in the mean total symptom score change, but showed a trend of higher responder rates (patients experiencing a clinically relevant improvement of at least 1.00 in the mean total symptom score) after four months of treatment with PPS compared to placebo. Likewise, the study reported by Sant et al 2003 did not show a significant benefit versus non-PPS treatment (placebo and hydroxyzine), only a trend. The last study Nickel et al 2015, which was performed by the current clinical standards and an up-to-date methodology failed to show any benefit in comparison to placebo and no statistically difference was reached between the 300 mg of PPS per day in comparison to 100 mg of PPS per day. These latter two studies were performed in countries where PPS was already available which lead to recruitment issues and to inclusion of non PPS naïve patients or non-responders to previous PPS therapy or patients with milder symptoms as patients with severe symptoms could have a direct access to the treatment.

The beneficial effect of PPS in interstitial cystitis (IC) was only shown in the 3 pivotal studies which used traditional diagnostic approach (Parsons and Mulholland, 1987; Mulholland et al., 1990; Parsons et al., 1993) but not in Sant et al., 2003 study and the studies using less specific IC definition (IC/BPS) as it was in the Holm-Bentzen et al., 1987 study and in the most recent Nickel et al., 2015 study. The response rate of a subgroup of patients with IC (2X to 3C) included in a post-HOC analysis in Nickel et al study were better for placebo (50%) than PPS 100 mg/day (30.3%), 100 mg x3/ day (34.5%).

However, interpretation of the data from the Nickel study is difficult given the severe limitations with regards to difficulties in patient enrolment, early termination, study design, enrolment of patients previously treated with PPS, severe recruitment problems and high dropout rates used for the analysis of efficacy.

Regarding the most pronounced and unexpected outcome of the post-hoc subgroup analysis reported by Nickel et al., 2015 the response rate of 50% in the placebo subgroup based on a 30% ICSI score improvement, such high placebo response rate was not observed in any other pivotal study and has to be taken as a clear indication for the multifactorial biases impacting the study results (patients with milder IC entering during a symptom flare, regression to the mean, introduction (inadvertent or not) of conservative therapy, which accentuated the benefits of placebo, and failure of clinical sites to keep patients in the trial). It should be noted that a high placebo response rate was also observed in the whole study: 40.7% (versus 39.8% for patients treated with 100 mgX1/day and 42.6% in those treated with 100mgX3/day) at 24 weeks.

To justify the abnormal high placebo response rate, the applicant provided the results of 2 other placebo-controlled studies performed in patients with IC (2X to 3C) diagnosed with cystoscopy and the response rates of the patients treated with placebo are about 12% (Warren et al., 2000) and 16% (van Ophoven et al., 2004) which correspond to the placebo response rates of the other pivotal studies (12.5-17.7%). Therefore, it can be concluded that the severe limitations of the study published by Nickel and colleagues in 2015, could have impacted the validity and usability of the study results overall.
Given the severe limitations of the Nickel et al study, it is agreed that its results could not be taken into account for meta-analysis. In addition, the results of Holm-Bentzen study are difficult to interpret as the GRA was not used as primary endpoint.

- **Results of the meta-analysis**

Several meta-analysis were performed by the applicant – primary endpoints meta-analysis (based on GRA improvement, both for ITT and non-ITT principles), sensitivity analysis (based on more homogenous patient population of four studies) and co-primary meta-analysis (evaluating the responder rates based on the pre-defined primary endpoints per study). Statistical methods for meta-analysis were used properly. However, the presentation was not fully consistent. Consideration of missing results as failures is adequate. In general, statistical methods used for meta-analysis were appropriate. The applicant provided the number of patients and the responder rates in the forest plot. These data confirm that responder rates were adequately estimated in ITT populations as defined in the meta-analysis without any loss of patients. Responses for pooled PPS and pooled placebo groups are missing but it seems that this information is available in the material provided for the additional meta-analysis conducted by the Applicant. The applicant provided the response levels for pooled PPS and pooled placebo in the meta-analysis.

In the primary meta-analysis conducted by the applicant, the estimated benefit differences in overall improvement are **12.4%** both for the ITT approach and the as reported approach. This primary meta-analysis included all 6 studies performed between 1987 and 2015. The clinical benefit estimate increased to **17%** in the sensitivity analysis when excluding the 2 pivotal studies (Holm-Bentzen and Nickel studies) which presented the lowest response rates and included a less homogeneous population than in the four other pivotal studies (mixing both broad IC/BPS).

These benefit differences mainly driven by the two pivotal studies Parsons et al 1993 and Mulholland et al 1990 for the drug approval of Elmiron in the US and by an earlier study (Parsons and Mulholland

1987) which met their primary endpoints seem relatively low and the studies were performed with old methodological standard requirements and with a low number of patients. Furthermore the most recent study (Nickel et al 2015) with up-to-date methodology provided un-conclusive results (and negative results in the subgroup of patients meeting the NIDDK criteria).

Thus, the applicant provided a new meta-analysis which took into account the results of the post Hoc analysis of the Nickel et al study in the subgroup of patients with IC (2X to 3C). Compared to the sensitivity analysis including only the four pivotal studies, which included the pre-defined homogeneous patient population of IC patients characterized by either glomerulations or Hunner's lesions, the estimated benefit difference in success rates decreased from **17.0% to 13.3% where this smaller difference is still statistically significant (p=0.007)**.

The CHMP took into consideration the unmet medical need for pharmacotherapy in this disease which can be invalidating in its severe forms and the ad hoc expert group confirmed that also small improvement could be considered as a clinical relevant benefit.

Furthermore given the severe limitations of the Nickel et al study (patients with milder IC entering during a symptom flare, regression to the mean, introduction (inadvertent or not) of conservative therapy, which accentuated the benefits of placebo, and failure of clinical sites to keep patients in the trial), CHMP considered that its results should not be taken into account in the meta-analysis.

Overall, the meta-analysis which combined the response rates of the four pivotal studies with patients meeting the ESSIC classification 2X to 3C which showed a benefit difference of 17% (PPS versus placebo), was taken into consideration to demonstrate the efficacy of PPS in the approved indication.

- **Key secondary endpoints**

The secondary endpoints were only considered supportive but pain and urgency were considered as the key main symptoms.

Overall, based on the results of 3 pivotal studies (Parsons and Mulholland 1987, Mulholland et al 1990 and Parsons et al 1993) an effect on ***pain*** (~44 vs 15 to 18%), ***urgency*** (~50 vs ~20%) and ***frequency*** (~60 vs 40%) but **not** on alleviating ***nocturia*** was shown. This was not the case in Sant et al., 2003 study and the studies using less specific IC definitions (IC/BPS) (Holm-Bentzen et al., 1987 and Nickel et al., 2015 studies).

The supportive meta-analysis conducted by the applicant mainly used the reported effect size on the symptoms pain and urgency and calculated the effects sizes on the ITT population as main outcome. Regarding these symptoms, this supportive meta-analysis reached statistically significant benefit differences in line with the primary meta-analysis evaluating the global response assessment (GRA) whatever the approach (ITT or as reported or sensitivity analysis).

- **Dose finding**

The majority of patients in the pivotal studies as well as in the supportive studies were treated with the established dose of 3x100 mg PPS per day and few patients received a very comparable dose of 2x200 mg PPS per day. The treatment duration was ranging from 3 months to 6 months.

Two dose-ranging studies evaluated a potential dose-response relationship (Nickel et al., 2005, Nickel et al., 2015) and came to the conclusion that neither a reduction of the dose to one third (1x100 mg PPS per day) nor a duplication or triplication of the dose (3x200 mg or 3x300 mg PPS per day) leads to statistically significant differences in the efficacy. It is agreed by the CHMP that the dose regimen should be 100 mgx3/ day as applied in the pivotal trials.

Additional expert consultation

At day 180 of the procedure the efficacy of elmiron was considered not being sufficiently demonstrated despite its well established use and international and European guidelines recommending pentosane polysulfate sodium for the treatment of IC for more than 10 years.

Therefore the CHMP decided to consult clinical experts in the disease adopting the following questions (Responses given by the ad hoc expert group are also outlined below):

1) Please discuss the definition (s) of IC / pain bladder syndrome and what is known about the etiology and pathogenesis of this condition. Which are the available treatment alternatives? Is there an unmet medical need for new treatments?

Chronic pelvic pain can have multiple reasons which may be deriving from within the bladder (e.g. chronic inflammation of the bladder region, characterized by Hunner's lesions / Glomerulations) or from outside the bladder (e.g. pudendus neuralgia); BPS is a diagnosis of exclusion. For the definition of BPS (and former IC) the experts referred to the ESSIC classification (Engeler et al 2015). It was considered that the IC definition at the time when most of the pivotal studies were performed would, as per todays classification, fall under BPS type 2 – 3.

Considering today's classification and medical practice an indication today would therefore need to refer to BPS.

The experts further emphasized that a categorization reflecting current clinical practice would refer to symptomatic severity and modern clinical trials would be designed to measure patient related outcomes. It was noted that particular intravesical changes such as Glomerulations and Hunner's lesions are not correlating with clinical severity of this condition.

The medical need for effective treatments in this condition was clearly seen by the experts. Current oral pharmacological treatment options are second line (after behavioral modifications and stress management) and comprise amitryptilin, cimetidine, hydroxyzine and PPS, PPS having a particularly benign safety profile. All treatment to date is symptomatic and none of above treatments is authorized in the EU in this condition.

2) Considering the results of the four pivotal studies, the results of Holm-Bentzen et al. (1987) and Nickel et al. (2015) studies and the European and international treatment guidelines of this condition, do you think that the available data support that PPS (Pentosan Polysulfate Sodium) has a place in the treatment of interstitial cystitis (IC)?

There was consensus about the weak evidence on efficacy of PPS deriving from the older studies showing a limited treatment effect. With regards to the more recent Nickel at al. (2015) study some experts were concerned about the efficacy results and would not use PPS as monotherapy, others were rather content to view results of this study as an outlier in terms of efficacy.

There was no consensus about the use of PPS in the patient population to be treated in clinical practice. Some experts would, depending on the patients risk profile, consider PPS due to its benign safety profile as a treatment option before invasive diagnostics. Other experts would use the drug due to the low level of evidence on efficacy and BPS being a diagnosis of exclusion only after full diagnostic workup to exclude confusable diseases and preferably in combination therapy.

The experts broadly agreed that study results from a population of BPS 2-3, a population difficult to treat, would be generalizable to patients suffering from other BPS categories.

There was broad agreement that more contemporary data on efficacy would be welcome to better define the use of the drug in today's clinical medicine.

3) Given the response rates in the subgroup "classical IC" in the Nickel et al study, do you consider the benefit difference 17% response rate (PPS versus placebo) based on a meta-analysis which combined the responses rates from the four pivotal studies with patients with "classical IC") as clinically relevant?

The experts considered that any response rate superior to placebo could be clinically relevant considering that there is no drug treatment authorized in this condition. The methodological weakness of the older trials was perceived as caveat for reliable interpretation of the efficacy of the product and the meta-analyses were considered of limited value due to different trial designs throughout publications. With regards to the Nickel study it was noted that many patients discontinued the trial. A reason for this could be the need for more effective pain treatment. The patient representatives emphasized that more robust data generation and definition of the patient population which benefits most from the drug would be welcome to spare the patient to try unsuccessful treatments but also the burden of invasive diagnostics was acknowledged. Also the high fluctuation and subjectivity of symptoms was acknowledged by the experts as a caveat for designing a trial in this condition.

4) If you find the available data supportive, which type of IC patients, taking into consideration the ICSI score or other criteria, would benefit from treatment with PPS?

In Europe PPS is often used off label and on a named patient basis. Whereas the French and the Belgian experts tended to prescribe PPS without full invasive diagnostic workup depending on the patients profile, experts from UK and Germany would use it after full exclusion of confusable diseases and mostly in combination therapy. A re-evaluation of the patient's response after 6 months of treatment would allow minimizing the risk of exposing patients who do not respond in the long term.

In summary the data of the pivotal studies suggest to use PPS in patients suffering from BPS with verified cystoscopic findings including hydrodistention and some experts emphasized that cystoscopy including hydrodistension is needed to display all glomerulations / Hunner's lesions and, at symptom persistence sooner or later cystoscopy would need to be done to finalize the diagnostic workup for this indication. Also hydrodistension (usually under general anesthesia) could induce symptom amelioration in some patients.

However experts also stressed the high burden of this workup for both the patient and the healthcare system cystoscopy being extremely painful and sometimes not useful in symptomatic patients. Cystoscopic findings for a decision to initiate PPS were considered of limited value in particular in symptomatic patients with low risk of important confusable diseases, such as bladder stones and cancer (e.g. in young women).

In particular the experts emphasized that there is no reason to believe that PPS is not effective in patients without glomerulations / Hunner's lesions as these morphological changes do not correlate with symptom severity. A restriction of the indication would also hardly be respected by clinicians considering the much broader well-established use of the product. Experts therefore were not in agreement to refer to these changes within a BPS indication. An indication statement adapted to clinical practice would rather refer to the severity of the condition.

5) Please discuss the most appropriate name of the condition and exactly which patients would be included in this condition. In particular the use of the terms bladder pain syndrome and interstitial cystitis should be explained as this will assist the COMP in understanding how the condition is currently defined by the medical profession.

In line with the answer to CHMP question 1, the expert group considered the term interstitial cystitis (IC) to be outdated and according to today's classification and medical practice the condition should be referred to as BPS. The experts concluded that IC correlates to a patient population with BPS type 2 – 3 and in particular 3C (characterised by Hunner's lesions); these BPS subtypes are, according to ESSIC

classification to be verified by cystoscopy including hydrodistension. IC represents therefore a subcategory of the condition BPS.

6) The prevalence in the literature is reported to have a range between 0.6% and 3% of the population when the term bladder pain syndrome is used. This is a very broad range, and is at variance with the prevalence proposed by the applicant, who is using the strict definition of interstitial cystitis and concludes on a number of 1.8 in 10,000 in Europe. The COMP would like to ask the expert group to consider which prevalence value is closer to the real situation in Europe for the condition as defined in question 1.

The experts agreed that if BPS is used the prevalence would be higher than what has been suggested by the sponsor. There were some concerns about the publications overestimating the incidence of BPS as they were based on questionnaires which only recorded the symptoms over one month. The experts were of the opinion that patients with BPS type 2 and 3 are not common. This was supported by a recent publication from 2015 (T.Bschleipfer et al. Interstitielle Zystitis/Blasenschmerzsyndrom, Urologische Infektiologie, 2015, 265-276) which considered that based on current literature the prevalence of BPS is 52-500 / 100.000 in women and 8-41 / 100.000 in men. Considering that about 10% of BPS patients have cystoscopic findings IC as defined as BPS type 2 and could still be under the threshold of 5 in 10,000.

2.5.4. Conclusions on the clinical efficacy

The applicant provided six pivotal studies to support this application. Only 3 pivotal randomized double-blind multicentre placebo controlled studies (Parsons and Mulholland 1987, Mulholland et al 1990 and Parsons et al 1993) among the 6 pivotal studies met their primary endpoint “GRA” and some secondary endpoints such as pain.

Based on the primary meta-analysis conducted by the applicant including the six pivotal studies, the estimated benefit differences reached about 13% (ITT and as reported). This benefit difference (PPS versus placebo) reached 17% when excluding 2 pivotal studies (Holm-Bentzen et al 1987 and Nickel et al 2015) with the lowest response rates and with a population less homogeneous than in the four other clinical studies (mixing both broad IC/BPS). Indeed, this benefit difference was mainly driven by the statistically significant results of the three pivotal studies Parsons et al 1993, Mulholland et al 1990 and Parsons and Mulholland 1987 including patients falling within ESSIC classification 2X to 3C.

Given the heterogeneity of the population included in Holm-Bentzen et al 1987 and Nickel et al and the clear efficacy results when pooling the remaining four pivotal studies including patients diagnosed IC falling within the ESSIC (BPS) classification 2X to 3C, it was agreed to refer in the indication to patients diagnosed IC / BPS using the traditional approach including cystoscopy with or without hydrodistension showing either glomerulations or Hunner’s lesions.

Furthermore according to the meta-analysis of the four pivotal studies performed in patients meeting the ESSIC classification 2X to 3C the pooled response rate under PPS treatment was 2-fold higher than the pooled response rate under placebo (“GRA” primary endpoint and also pain and urgency)and efficacy of PPS was considered sufficiently demonstrated in this population.

The term BPS rather than interstitial cystitis (IC) was put forward by the International Society for the Study of BPS (ESSIC) and is currently used in the guidelines and by the experts. Therefore the applicant agreed to amend the applied therapeutic indication to:

"Elmiron is indicated for the treatment of bladder pain syndrome characterized by either glomerulations or Hunner’s lesions in adults with moderate to severe pain, urgency and frequency of micturition (see section 4.4)"

2.6. Clinical safety

The safety of elmiron capsules was evaluated from scientific publications on six pivotal, placebo-controlled clinical studies as well as in supportive active-controlled or uncontrolled studies. No clinical safety studies with elmiron were performed by the applicant, in accordance with Article 10a of Directive 2001/83/EC (well-established medical use).

Patient exposure

561 patients were exposed to PPS in the six pivotal, placebo-controlled trials (Holm-Bentzen 1987; Parsons and Mulholland 1987; Mulholland 1990; Parsons 1993, Sant 2003 and Nickel 2015). 3407 patients were exposed to PPS in supportive active-controlled or uncontrolled studies (Nickel 2005; Ophoven 2005; Davis 2008; Sairanen 2005; Fritjofsson 1987 and Hanno 1997). 124 patients were exposed to PPS in two cohort studies (Waters 2000 and Jepsen 1998).

192 patients were exposed to PPS at least 6 months (corresponds to 1152 patient-months) in the (pivotal) clinical trials. Most patients were exposed to 300 mg PPS per day (234 patients), some were exposed to 400 mg PPS per day (52 patients).

429 female patients and 29 male patients were exposed to PPS in the (pivotal) clinical trials.

Overall, more than 3,500 patients were exposed to PPS in published clinical studies evaluating the safety and efficacy of PPS for the treatment of IC. In these studies, subjects mainly administered the established oral dose of 3x100 mg PPD per day, but also the threefold dose (3x300 mg PPS per day) was evaluated. The exposure in the studies covered periods of more than 3 years treatment with PPS.

Adverse events

Holm-Bentzen et al. (1987) reported that 5 patients receiving active drug complained of **peripheral oedema.** One patient had a skin rash that probably was related to PPS treatment. The applicant assumed that the same case of skin rash is mentioned twice in this publication. Among the 62 patients, who completed the study reported by Parsons and Mulholland (1987) only one single side effect **(skin rash)** was reported.

In the study published by Fritjofsson et al. (1987), **diarrhoea** was reported in 6 patients and one patient complained of **dyspepsia** during treatment. **Swelling of legs** occurred in 2 patients. Mulholland et al. (1990) and Parsons et al. (1993) described the occurrence of adverse reactions in the safety sections. The Applicant explained that the incidence of adverse reactions observed in both studies were low in both treatment groups and the observed effects are not different from effects expected to occur in any random population over a three-month period. In Parsons et al. (1993) study, only digestive system events, *diarrhoea* or *nausea* were reported from more than one patient and occurred more often in the placebo group than in the PPS group.

Diarrhoea is reported with a frequency of 4.9% in the Nickel study (2015), 15% in the Waters study (2000) and in the Nickel study (2005) and 2.7% in the Parsons study. **Nausea** is reported with a frequency of 9.8% in the Nickel study (2015), 8% in the Nickel study (2005), 2% in the Mulholland study and 3.7% in the Hanno study. **Abdominal pain** is reported with a frequency of 7% in the Nickel study (2005). **Dyspepsia** is reported with a frequency of 2 to 4% depending on the study.

Alopecia, cited as reversible, is reported with a frequency of 3.9% in the Hanno study and 5% in the Nickel study (2015). Hair-thinning/hair loss is reported with a frequency of 11% in the Waters study.

Hair-thinning/alopecia are known adverse reactions associated with heparin treatment and it is thus not surprising to have these AEs described with PPS. **Headache** is reported with a frequency of 11.5% in the Nickel study (2015), 2.9% in the Hanno study and 2% in the Mulholland study. **Rectal bleeding** is reported with a frequency of 4 % in the Nickel study (2005). Bleeding events as rectal bleeding are related to the heparin-like structure of PPS.

Overall, hair-thinning/hair loss/alopecia and gastro-intestinal disorders (e.g. diarrhea, abdominal cramping, nausea and dyspepsia) were the most frequently reported adverse reactions with PPS in the literature.

Serious adverse event / deaths / other significant events

Serious adverse events

No treatment-related SAEs were reported in the clinical studies with PPS capsules. PPS is a highly sulfated glycosaminoglycan comparable to heparin and systemically available PPS has relevant anticoagulant activity. Some cases of thrombocytopenia occurring during parenteral PPS treatment and mimicking the heparin-induced thrombocytopenia syndrome have been reported, especially in the French literature (Tardy-Poncet et al., 1994), thus any potential effects of oral PPS treatment on the coagulation system would be considered as an AE of special interest. The case of a 28-year old patient with Interstitial Cystitis was reported by Strohmaier et al. (1987) in the context of the evaluation of glycosaminoglycan excretion. This patient received 750 mg/day PPS in order to increase the glycosaminoglycan excretion, which was reduced based on his underlying disease. The patient developed haematomas spontaneously and macrohaematuria. No further information is provided.

Given the weak anticoagulant effect of PPS, PPS could have favored the apparition of haematoma in two published cases of serious AEs:

- An **epidural hematoma** reported in a woman receiving lumbar epidural steroid injection (Siddiqui et al.2001). In addition to PPS, the woman was treated with 300 mg gabapentin three times a day and 25 mg amitriptyline orally at night. The authors concluded, that this patient's epidural haematoma was related to either PPS or it might have been a direct consequence of multiple needle punctures. However, the Applicant explained that an extensive epidural haematoma that leads to neurologic symptoms is unlikely to arise from needle trauma alone.
- A **neck hematoma** reported in a woman after an attempted internal jugular catheter insertion (Gill et al. 2002) and oral administration of PPS in doses of 3x300 mg PPS per day for at least 4 months.

No alteration of coagulation parameters have been reported in a small PD study on 18 healthy volunteers after administration of oral doses of 1500 mg PPS.
As limited information is available on use in patients concomitantly using anticoagulants, undergoing invasive procedures or in patients with increased risk of bleeding, these patients should be evaluated carefully for hemorrhage when taking PPS. Therefore, the applicant added:

- a contra-indication in section 4.3 of the SmPC: "*due to the weak anticoagulant effect of pentosan polysulfate sodium, Elmiron must not be used in patients who actively bleed. Menstruation is no contraindication*" and

- a warning in section 4.4 of the SmPC: "*Pentosan polysulfate sodium is a weak anticoagulant. Patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding (due to other therapies such as coumarin anticoagulants, heparin, t-PA,*

streptokinase, high dose acetylsalicylic acid, or nonsteroidal anti-inflammatory medicinal products) should be evaluated for hemorrhage".

- An interaction in section 4.5 was also added : "*Due to the weak anticoagulant effect of pentosan polpysulfate sodium, patients, who are concomitantly treated with coumarin anticoagulants, heparin, t-PA, streptokinase, high dose aspirin, or nonsteroidal anti-inflammatory drugs should be evaluated for hemorrhage*."

A single case report of **cerebral sagittal thrombosis** after oral administration of PPS for the treatment of Interstitial Cystitis was reported in scientific literature (Rice et al., 1998): the patient received a low dose oestrogen as oral contraceptive and it is known that thrombotic risk is higher during the first year of contraceptive use, however the treatment was introduced for a long time at the time of the event (8 years). On the contrary, PPS was only introduced for 3 weeks at the time of the event. No information on decreased platelet counts is available as an indication for thrombocytopenia (blood counts only have been evaluated 2-weeks after stopping PPS administration and were normal). A modest titer anti-heparin platelet factor 4 antibody was found but the relevance and sensitivity of this ELISA test for PPS-induced antibodies is questionable. PPS-induced thrombocytopenia comparable to heparin-induced thrombocytopenia cannot be excluded. It should be noted that some cases of thrombocytopenia occurring during parenteral PPS treatment and mimicking the heparin-induced thrombocytopenia have been reported.

Deaths

7 deaths were reported in a long-term, open-label study (Hanno et al. 1997), considered as not related to study medication. 3 deaths were reported in the study published by Jepsen et al. (1998), considered as not related to study medication.

Laboratory findings

No changes in blood and urinary samples were noted during the trial reported by Holm-Bentzen et al. (1987). The investigations performed before and after the trial included urine culture, urine cytology, urinary. There were no abnormal serum tests, including prothrombin time, partial thromboplastin time, lactic dehydrogenase, serum glutamic oxaloacetic and pyruvic transaminases, haematocrit or white blood count reported by Parsons and Mulholland (1987). A transient increase in a γ-glutamyl-transferase was observed in 4 out of 87 patients without clinical manifestation (Fritjofsson et al., 1987). As reported by Mulholland et al. (1990) there were no differences between the treatment groups in terms of clinically significant changes in any of the laboratory data. One patient in the PPS-treated group had SGOT and SGPT values of 118 and 133 at three months compared with 56 and 115 at baseline respectively. There were no clinically relevant differences between the treatment groups for any of the laboratory data and there were no laboratory findings outside the normal range for any of the parameters measured in the study reported by Parsons et al., 1993. 25 months because of increasing SGOT and SGPT, which was verified by re-challenging with PPS. Another patient had increased AST after 5.5 months but stopped taking PPS because of no effect. One patient had increased creatinine levels of 2.2 mg/dl after 10.5 months but discontinued PPS because IC symptoms continued. There were no cases with laboratory measures critically outside the normal limits and related to the trial intervention in the study reported by Davis et al. (2008). No clinically meaningful change was noted in clinical laboratory tests, vital signs or physical examination in the study reported by Nickel et al. (2015).
According to the applicant, the laboratory data were not reported quantitatively at all or only qualitatively or as individual cases.

Coagulation findings. Number of previous studies showed a risk for coagulopathy after oral administration (Gaffney et al., 1986) both after single and multiple dosages, and both in clinical and in non-clincial settings (Marsch et al 1985). See **Figure 5** below.

Figure 3The fibrinolytic responces to oral PPS (Gaffney et al., 1986)

Single dose effect	**Multiple dose effect**

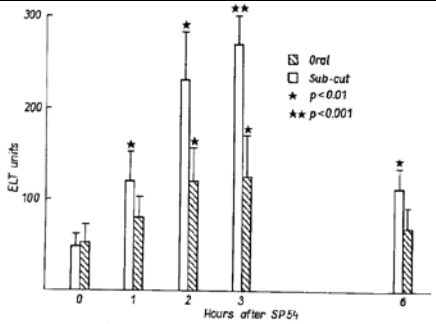
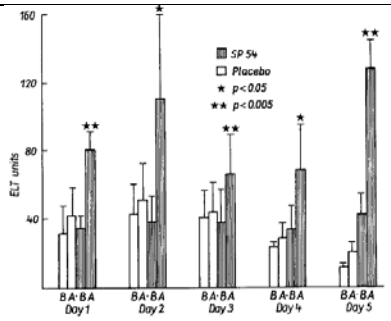

	

Fig. 4. The effect of SP54 given orally (500 mg) and s.c. (50 mg) on euglobulin lysis time (ELT) activity units (mean ± SEM, $n = 6$, significance as shown calculated by paired t-test)	Fig. 5. The effect of repeated doses of SP54 given orally (500 mg/day) on euglobulin lysis time (ELT) activity units (mean ± SEM, $n = 6$, significance as shown in diagram calculated by paired t-test). B before treatment, A 2 h after treatment

In particular, one observation in Davis et al., 2008 study cannot be neglected: ~40% of blood clotting tests (prothrombin time, partial thromboplastin time, and platelet count) were outside normal ranges for both oral PPS and oral plus intravesicular PPS. These findings are in line with several other findings of possible impact on coagulation of oral PPS, such as reported rectal bleeding. According to the applicant, the literature case reports and cases from the studies, are arguing that the issue is very controversial as the most informative study (Faaij et al., 1999), which used relevant monitoring tests (aPTT, Anti-Xa activity, t-PA activity and fibrin plate lysis) did not detect such effects after oral PPS at very high dosage (1500 mg PPS) in comparison with IV administration. Thus, it is reasonable to conclude that rectal bleeding is a clinically significant AR but does not preclude the need to inform prescribers about clinical importance of the other coagulopathies adverse reactions reported in post marketing even with a low frequency. Therefore, this “class effect” has been mentioned in the SmPC. The AE “Coagulation disorders” has been added in section 4.8 of the SmPC to reflect the reporting of laboratory parameters.

Safety in special populations

Children

No information on paediatric patients is reported in the scientific literature. The disease is nearly not existent in the paediatric population. The medicinal product will be indicated for the treatment of adult patients with Interstitial Cystitis.

Elderly

The Applicant did not perform a safety analysis based on age. The average age of the patients was above 40 years in the literature (from 42.7 to 63 years depending on the study). Patients up to 80 years were included in the clinical trials.

Pregnant or breast feeding women

Pregnant or breast-feeding women were excluded from enrolment into the pivotal clinical trials. Systemic bioavailability of PPS after oral administration is very limited, accordingly, exposure of a foetus or excretion into milk is very unlikely.

A study in eight pregnant women who had a planned abortion was conducted to generate data on the

trans placental passage of PPS (Forestier et al., 1986). The data generated in this study provide no indication of trans-placental passage of PPS.
Since no further data from clinical studies with PPS in pregnant or nursing women are available, the Summary of Product Characteristics (SmPC) states that PPS capsules should not be used during pregnancy or lactation unless clearly necessary.

Patients with renal or hepatic impairment
No specific information on patients with renal impairment is reported in the literature.
Because there is evidence of hepatic and renal contribution to the elimination of pentosan polysulfate sodium, hepatic or renal impairment may have an impact on the pharmacokinetics of pentosan polysulfate sodium. As stated in the product information patients with relevant hepatic or renal insufficiency should be carefully monitored when treated with pentosan polysulfate sodium.

Immunological events
In a single case of cerebral sagittal sinus thrombosis after oral administration of PPS (see above), no indication of antibody formation was observed except a modest positive response received in an ELISA-assay for anti-heparin platelet factor 4 antibodies. The relevance and sensitivity of this ELISA test for PPS-induced antibodies is questionable.

Safety related to drug-drug interactions and other interactions

Evaluable information on interactions is limited to the information provided in the literature.

Drug-drug interactions between PPS and warfarin were evaluated in an open-label study (Modi et al. 2005). PK parameters of warfarin and INR were similar in the absence and presence of PPS. Pentosan polysulfate sodium is a weak anticoagulant. Patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding (due to treatment with other medicinal products influencing coagulation such as anticoagulants, heparin derivatives, thrombolytic or antiplatelet agents including acetylsalicylic acid, or nonsteroidal anti-inflammatory medicinal products should be evaluated for haemorrhagic events. Patients who have a history of heparin or pentosan polysulfate sodium induced thrombocytopenia should be carefully monitored when treated with pentosan polysulfate sodium. This is reflected in a warning in section 4.5 of the SmPC, with a cross-reference to section 4.4.Discontinuation due to adverse events.

Holm-Bentzen et al. (1987) reported that 2 patients in protocol A stopped the medication because of headache, nausea and dizziness and in protocol B one patient stopped medication because of a skin rash after 2 weeks and another one stopped because of aggravation of bladder symptoms. No information is provided, whether these patients stopping medication during the study were treated with PPS or placebo. Out of the 87 patients enrolled in study published by Fritjofsson et al. (1987), 7 patients terminated treatment early due to AEs (2 patients due to swollen legs and gastrointestinal distress, respectively; urinary infection in one, dysphagia in one, anaemia in one).

In the report of Parsons et al. (1993), 3 patients in the PPS group and 5 patients in the placebo group discontinued treatment due to AEs. In the compassionate use study reported by Jepsen et al., (1998) 16/97 patients stopped taking PPS due to AEs. The majority of those (81.6%) stopped therapy during the first 6 months. Waters et al. (2000) reported about the retrospective analysis in 27 patients treated with PPS for at least 8 weeks; 4 patients (15%) stopped taking PPS because of side effects including diarrhoea, abdominal cramping, nausea, hair thinning. Symptoms worsened in 2 patients (9%) of the patients, forcing discontinuance. In the study reported by Sant et al. (2003), a total of 10 patients (8%) withdrew from study due to adverse events. Nickel et al. (2005) reported that in the

dose-ranging study evaluating daily oral administration of 300, 600 and 900 mg PPS for up to 32 weeks, 150 patients (39.5%) discontinued treatment before the end of this study. Of them, 22.4% did so because of AEs (primarily diarrhoea and abdominal pain). AEs were the reason for discontinuation of treatment in 18%, 16.8%, and 30.7% of patients taking 300, 600, and 900 mg PPS, respectively, and this was dose dependent ($p<0.05$). In the study reported by Nickel et al. (2015), AEs, which were mostly gastrointestinal, led to the withdrawal of 12 patients (10.2%) in the placebo group, 17 (13.3%) in the PPS 100 mg group and 14 (11.5%) in the PPS 300mg group. The applicant provided safety findings for discontinuations due to AEs for separate studies but without critical cumulative review. In particular, they are related to rather limited local GI tolerance. In one of the studies (Nickel et al 2005), these AEs were dose dependent.

Post marketing experience

The oral PPS is approved in Canada since 1993, Australia since 1994 and US since 1996. The SmPC has been modified to reflect the AEs listed in Canadian, Australian and US SmPCs, including post-marketing data.

2.6.1. Discussion on clinical safety

The safety of PPS capsules was evaluated from scientific publications on the six pivotal, placebo-controlled clinical studies as well as in supportive active-controlled or uncontrolled studies.
Overall, more than 3,500 patients were exposed to PPS in published clinical studies evaluating the safety and efficacy of PPS for the treatment of IC. In these studies, subjects mainly administered the established oral dose of 3x100 mg PPD per day, but also the threefold dose (3x300 mg PPS per day) was evaluated. The exposure in the studies covered periods of more than 3 years treatment with PPS.

The applicant provided a thorough compilation of the patient exposure for safety analyzing separately placebo-, active-controlled, open studies and compassionate use for patients exposed to PPS in general, to PPS with the proposed dose range and with long-term safety data. The applicant summarized that at least more than 4000 patients were exposed to PPS in studies and ~3800 to the proposed dose range (300 to 400 mg/day). The information submitted on long-term safety is limited (>6 month of therapy, exclusively from uncontrolled studies only).

No dedicated studies were performed in special populations. Elderly people were included in the pivotal studies. Pregnant or breast-feeding women were excluded from enrolment into the pivotal clinical trials. No specific studies were performed in patients with renal or hepatic impairment as the systemic bioavailability of PPS is very low (< 1%).

The ratio women/men was 10:1 in the pivotal studies, which is representative of the gender-based prevalence of the IC in the general population. Meanwhile, due to the very low number of male patients enrolled in the clinical trials, the RMP has been updated to add “use in male patient” as missing information in the summary of safety concerns table in order to collect safety data in men in post-marketing.
However, given the mode of action of PPS in the treatment of IC, the safety profile observed of PPS in the pivotal studies, it is agreed that there is no reason to expect a specific safety profile in men, as an impact on the male reproductive system is not expected. The only gender specific adverse event reported from clinical studies is “strong menstrual bleeding”.

Overall, hair-thinning/hair loss/alopecia and gastro-intestinal disorders (e.g. diarrhoea, abdominal cramping, nausea, and headache) were the most frequently reported adverse reactions with PPS in the

literature. Bleeding events as rectal bleeding are considered to be related to the heparin-like structure of PPS.
Several cases of serious bleeding AEs with PPS have been published in the literature: one case of epidural hematoma, one case of neck hematoma, one case of hematomas (location not specified). For two cases, a needle trauma was reported (steroid epidural injection and venous jugular catheter insertion) and PPS might have favoured the occurrence of bleeding as PPS has a weak anticoagulant effect (heparin-like substance).

Overall, although this relationship between risk of serious coagulopathies and oral PPS is not obvious, the coagulopathy is not excluded and could be plausible considering other bleeding effects observed after the oral PPS administration and in case of co-administration with other medicinal products influencing coagulation. The applicant accepted to include PPS-thrombocytopenia and haemorrhage as important potential risks into the updated RMP and to add a contra-indication in patients who actively bleed in section 4.3 of the SmPC, a warning in 4.4 on patients undergoing invasive procedures and other increased risk of bleeding and an advise in section 4.5 of the SmPC to evaluate for haemorrhagic events in case of concomitant treatment with anticoagulants. Furthermore the AE “Coagulation disorders” has been added in section 4.8 of the SmPC to reflect the reporting of laboratory parameters.

Several cases of elevated hepatic enzymes (SGOT and SGPT) have been reported. One case of increased creatinine levels has been reported, possibly linked to PPS (creatinine decreased after stopping treatment).
The AE “Liver function abnormalities” has been added in section 4.8 of the SmPC to reflect the reporting of laboratory parameters which is considered acceptable.

The applicant did not report immunological events except a case of cerebral sagittal sinus thrombosis, although no dedicated studies are presented. Allergic reactions which are considered as a “class effect” were added in the SmPC to inform about this class effect which may not have been observed directly in relation to the product.

Overall, adverse events led to discontinuation of the PPS treatment in a significant percentage of patients (about 8 to 18 % in the published studies). Lack of efficacy also led to discontinuation in a significant percentage of patients (7 to 56 % depending on the study). AEs leading to discontinuation were reported in up to 13.2% with a maximal incidence of 22.4%. Therefore it was added to 4.2 of the SmPC that response to treatment with pentosan polysulfate sodium should be reassessed every 6 months and that in case no improvement is reached 6 months after treatment initiation, treatment with pentosan polysulfate sodium should be stopped.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of PPS is not considered of concern. Due to the heparin-like structure of PPS, a weak anticoagulant effect was observed with PPS and patients with risk factors for increased bleeding (undergoing invasive procedures, having underlying coagulopathy or taking anticoagulants) should be carefully evaluated for haemorrhage during the treatment. This risk is adequately addressed in various sections of the SmPC and as important identified risk in the RMP.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Development of a pentosan polysulfate induced thrombocytopenia
	Development of haemorrhage
Missing information	Use in patients with hepatic impairment
	Use in patients with hepatic impairment
	Use in patients with renal impairment
	Use in pregnant women
	Use in breast feeding women
	Use in patients concomitantly using anticoagulants
	Use in patients with bleeding disorders
	Use in male patients

Pharmacovigilance plan

Not applicable, as no additional pharmacovigilance activities are proposed.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risk: Development of a pentosane polysulfate induced thrombocytopenia	Warning in section 4.4: Pentosan polysulfate sodium is a weak anticoagulant. Patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding (due to other therapies such as coumarin anticoagulants, heparin, t-PA, streptokinase, high dose aspirin, or nonsteroidal anti-inflammatory drugs) should be evaluated for hemorrhage. Caution should be exercised when using pentosane polysulfate sodium in patients who have a history of heparin or pentosan polysulfate induced thrombocytopenia.	None proposed
Important potential risk: Development of haemorhage	Warning in section 4.4: Pentosan polysulfate sodium is a weak anticoagulant. Patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding (due to other therapies such as coumarin anticoagulants, heparin, t-PA, streptokinase, high	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	dose aspirin, or nonsteroidal anti-inflammatory drugs) should be evaluated for hemorrhage. Caution should be exercised when using pentosane polysulfate sodium in patients who have a history of heparin or pentosan polysulfate induced thrombocytopenia.	
Missing information: Use in patients with hepatic impairment	Warning in section 4.4: Hepatic or renal insufficiency Pentosan polysulfate has not been studied in patients with hepatic or renal insufficiency. Because there is evidence of hepatic and renal contribution to the elimination of pentosan polysulfate, hepatic or renal impairment may have an impact on the pharmacokinetics of pentosan polysulfate. Caution should be exercised when using pentosane polysulfate in this patient population.	None proposed
Missing information: Use in patients with renal impairment	Warning in section 4.4: Hepatic or renal insufficiency Pentosan polysulfate has not been studied in patients with hepatic or renal insufficiency. Because there is evidence of hepatic and renal contribution to the elimination of pentosan polysulfate, hepatic or renal impairment may have an impact on the pharmacokinetics of pentosan polysulfate. Caution should be exercised when using pentosane polysulfate in this patient population.	None proposed
Missing information: Use in pregnant women	Information in section 4.6: There are no data from the use of pentosane polysulfate in pregnant women. As a precautionary measure, it is preferable to avoid the use of Pentosan polysulfate 100 mg hard capsules during pregnancy.	None proposed
Missing information: Use in breast feeding women	Information in section 4.6: It is unknown whether pentosane polysulfate or metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Pentosan polysulfate 100 mg hard capsules should not be used during breast-feeding.	None proposed
Missing information: Use in patients concomitantly using anticoagulants	Warning in section 4.4: Pentosan polysulfate sodium is a weak anticoagulant. Patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding (due to other therapies such as coumarin anticoagulants, heparin, t-PA, streptokinase, high dose aspirin, or nonsteroidal anti-inflammatory drugs) should be evaluated for hemorrhage. Caution should be exercised when using pentosan polysulfate sodium in patients who have a history of heparin or pentosan polysulfate induced thrombocytopenia.	None proposed
Missing information: Use in patients with bleeding disorders	Warning in section 4.4: Pentosan polysulfate sodium is a weak anticoagulant. Patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding (due to other therapies such as coumarin anticoagulants, heparin, t-PA, streptokinase, high	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	dose aspirin, or nonsteroidal anti-inflammatory drugs) should be evaluated for hemorrhage. Caution should be exercised when using pentosan polysulfate sodium in patients who have a history of heparin or pentosan polysulfate induced thrombocytopenia.	
Missing information: Use in male patients	None proposed, as there is no reason to expect a specific safety profile in men, as an impact on the male reproductive system is not expected. The only gender specific adverse event reported from clinical studies is “strong menstrual bleeding”	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 05 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Interstitital Cystitis (IC) is a chronic, debilitating disorder, distressing bladder condition, which is characterised by pelvic pain associated with bladder filling, pollakiuria with a voiding frequency of more than eight urinations per day and more than two urinations per night, cystoscopic lesions (petechiae, Hunner's ulcers) revealed by a bladder hydrodistention test, and/or histological anomalies such as inflammatory mononuclear cell infiltrates and tissue granulation, in the absence of infection or any

other pathology. The clinical picture is dominated by pain and pollakiuria. Although the pain is usually described as pelvic, it may also involve the perineum, vagina, suprapubically radiating to the groins, rectum, sacrum, scrotum and urethra. It becomes more severe upon bladder filling with relief after urination. The pollakiuria is the consequence of a nearly constant urge to urinate, which increases with bladder filling and is relieved by urination. 90% of the patients are afflicted women in their fifth and sixth decades of life. Symptoms often resemble those of patients with overactive bladder. Up to 50% of patients with symptoms of interstitial cystitis will have spontaneous resolution in time.

The diagnosis of IC is primarily one of exclusion, using symptoms, examination, urine analysis and urine culture (to rule out a urinary tract infection), cystoscopy with hydrodistension (to rule out bladder cancer, vesical stones, urethral diverticula and intravesical foreign bodies), and biopsy (to exclude other pathologies).

In the pivotal studies, the population was included with different IC definitions, mixing both broad **IC/BPS** (i.e. In European Holm-Bentzen et al. 1987 Study and in Canadian/US Nickel et al 2015 Study) or definitions falling within ESSIC BPS classification 2X to 3C (i.e. in Parsons and Mulholland 1987 Study, Mulholland et al 1990 Study, Parsons et al 1993 Study, and in Sant et al 2003 Study).

In accordance with the advice of the ad hoc expert group and the ESSIC classification (Engeler et al 2015) the CHMP considered that the definition of former IC at the time when most of the pivotal studies were performed would, as per todays classification, fall under BPS characterized by glomerulations or Hunner's lesions (BPS type 2X – 3C) and the applicant agreed to amend the indication accordingly. Furthermore pain is considered as the main key symptom of the disease and should be taken into consideration in the definition of the disease.

3.1.2. Available therapies and unmet medical need

All available treatment options thus far are purely symptomatic. There are no medicinal products approved for the treatment of IC in Europe. Current treatment options include:

•off-label enteral and parenteral use of medicinal products (analgesics, corticosteroids, anti-allergics, PPS, Hydroxyzine, Amitriptyline, antibiotics, immunosuppressants, Gabapentin, pregabalin, and quercetin)

•bladder hydro-distension

•intravesical application of medicinal products and medical devices (DMSO, PPS…)

•surgery

Therefor a medical need for approved treatment options in interstitial cystitis / bladder pain syndrome characterized by either glomerulations or Hunner's lesions exists given the fact that there are no medicinal products authorised for this condition in Europe.

3.1.3. Main clinical studies

The applicant provided literature on six randomised, double-blind, placebo-controlled studies as pivotal database to evaluate the efficacy and safety of PPS of which Mulholland et al 1990 and Parsons et al 1993 studies were the pivotal studies for MAA in USA and Canada.

All but one of 6 pivotal studies were conducted more than 10 years ago (except the more recent study of Nickel et al 2015). IC patients characterized by either glomerulations or Hunner's lesions (BPS type

2 – 3) were included in four of the pivotal studies (Parsons and Mulholland 1987, Mulholland et al 1990, Parsons et al 1993 and Sant et al 2003).

The study objectives were "prospective evaluation of PPS for the treatment of IC". Key study endpoints/outcomes in all 6 pivotal studies were patient-reported outcomes via patient responder analysis which is considered as a reasonable approach for a functional disease.

The patient population enrolled in the 6 pivotal studies varied between the studies and altogether was enrolling a broader BPS population. The majority of patients were Caucasian, female and the average age was above 40 years. The majority of the patients enrolled are Caucasians and considered representative for the EU population.

Within the 6 pivotal studies data on two dosage regimens was provided: either 100 mg 3 times a day or 200 mg 2 times a day. The treatment duration was ranging from 3 months to 6 months. The recommended dose is 300 mg/day taken as one 100 mg capsule orally three times daily with assessment of response to treatment every 6 months.

3.2. Favourable effects

Among the 6 pivotal studies, 3 studies (Parsons and Mulholland 1987, Mulholland et al 1990 an Parsons et al 1993) met their primary endpoint "**overall global improvement**" (assessed by a patients self-evaluation confirmed by an investigator's evaluation based on patients reporting at least 6 moderately improved or 7 markedly improved on 7 point numerical rating scale) and their key secondary endpoints such as pain in comparison to placebo. The 3 other studies (Holm-Bentzen et al 1987, Sant et al 2003 and Nickel et al 2015) did not meet their primary and their key secondary endpoints.

In the primary meta-analysis conducted by the applicant including all 6 pivotal studies published between 1987 and 2015, the estimated benefit differences in overall improvement were about **13%** with the two approaches (ITT or as reported).

This benefit difference was mainly driven by the pivotal studies Parsons et al 1993 and Mulholland et al 1990 for the drug approval of Elmiron in the US and by an earlier study (Parsons and Mulholland 1987) including patients falling within ESSIC classification 2X to 3C (patients with cystoscopic changes i.e. either glomerulations or Hunner's lesions). A 4th study enrolling patients falling within ESSIC classification 2X to 3C (Sant et al. (2003)) did not show a statistically significant benefit difference against placebo but a positive trend and was conducted in the US at the time when PPS (as Elmiron) was commercially available for the treatment of IC which lead to enrolment of patients previously treated with PPS. No beneficial effect was demonstrated in studies using less specific IC definition (Holm-Bentzen et al., 1987 and Nickel et al., 2015). Also the severe limitations of the Nickel et al study (patients with milder disease entering during a symptom flare, regression to the mean, introduction (inadvertent or not) of conservative therapy, which accentuated the benefits of placebo, and failure of clinical sites to keep patients in the trial) are acknowledged by the CHMP. In addition, the results of Holm-Bentzen study are difficult to interpret as the GRA was not used as primary endpoint.

The estimated benefit differences reached **17%** in the sensitivity analysis when excluding the 2 studies (Holm-Bentzen et al 1987 and Nickel et al 2015) which presented the lowest response rates and enrolled a broader and less homogeneous patient population.

The applicant provided a comparison of the definitions of the primary endpoints "GRA" and responder rates among all 6 studies and especially in the four pivotal studies. It is agreed that the responder rates used in the four pivotal studies enrolling a homogeneous and clear defined patient population

which is representative of the targeted patient population (Parsons and Mulholland, 1987, Mulholland et al., 1990; Parsons et al., 1993, Sant et al., 2003) are deemed comparable.

When considering the supportive meta-analysis on the key secondary symptoms “pain and urgency”, the benefit differences reached statistically significance (whatever the approaches ITT or as reported) in line with the primary meta-analysis evaluating the GRA.

It was therefore agreed with the applicant to base the indication on the more homogeneous population of the four pivotal studies including patients with BPS type 2 – 3 outlining in 4.1 of the SmPC bladder pain syndrome characterized by either glomerulations or Hunner’s lesions reflecting the patient population in which clinical efficacy was demonstrated.

3.3. Uncertainties and limitations about favourable effects

The beneficial effect of PPS was mainly driven by the pivotal studies including patients falling within ESSIC classification 2X to 3C whereas no beneficial effect was demonstrated in studies using less specific IC / BPS inclusion criteria for patients. Also, the mechanism of action of PPS is currently not totally understood and only 1% of the orally administered PPS is absorbed.

The term “BPS” should be used rather than interstitial cystitis (IC). Indeed, the term BPS was put forward by the International Society for the Study of BPS (ESSIC) and is currently used in the guidelines and by the experts. Whereas a beneficial effect, as outlined by the ad hoc experts, might be generalizable to other BPS types, robust data on this effect are missing. In accordance with the experts view, it was also taken into account by the CHMP that the definition of a target population which benefits most from the drug would avoid to try unsuccessful treatments.

Given uncertainties about the favourable effects of elmiron in a broader BPS population the approved indication refers therefore to patients diagnosed with bladder pain syndrome characterized by either glomerulations or Hunner’s lesions using traditional diagnostic approach including cystoscopic examination with or without hydrodistension which corresponds to the population included in the four pivotal studies (Parsons and Mulholland 1987, Mulholland et al 1990, Parsons et al 1993 and Sant et al 2003) in which the efficacy was robustly demonstrated (in three of these studies the primary endpoint reached statistical significance).

3.4. Unfavourable effects

Hair-thinning/hair loss/alopecia and gastro-intestinal disorders (e.g. diarrhoea, abdominal cramping, and nausea, headache) were the most frequently reported adverse reactions with PPS in the literature. The most common adverse events reported from the clinical studies are headache, dizziness and gastro-intestinal events like diarrhoea, nausea, abdominal pain and rectal bleeding.

Cases of serious bleeding AEs with PPS have been published in the literature: one case of epidural hematoma, one case of neck hematoma, one case of hematomas (location not specified). For two cases, a needle trauma was reported (steroid epidural injection and venous jugular catheter insertion) and PPS might have favoured the occurrence of bleeding as PPS has a weak anticoagulant effect (heparin-like substance).
It was therefore concluded that due to the heparin-like structure of PPS, a weak anticoagulant effect might be observed with PPS and patients with risk factors for increased bleeding (undergoing invasive procedures, having underlying coagulopathy or taking anticoagulants) should be carefully evaluated for haemorrhage during the treatment as it is mentioned in section 4.4 of the SmPC. Furthermore PPS-

thrombocytopenia and haemorrhage was included as important potential risks into the RMP and a contra-indication in patients who actively bleed.

Regarding the potential immunological ADRs, the applicant explained that there might be different reasons for immunological ADRs and agrees that in some cases, allergic reactions related to PPS could be the cause (in case of skin rash). Therefore, the applicant included the AEs “rash” and “allergic reactions” into section 4.8 of the SmPC. Overall the safety profile of elmiron is considered not of concern.

3.5. Uncertainties and limitations about unfavourable effects

PK has not been studied in some of the special populations (elderly patients, hepatically or renally impaired patients, paediatric patients, pregnant and breast feeding women) and the lack of this data as well as precautionary statement are reflected in the SmPC.

The ratio women/men was 10:1 in the pivotal studies, which is representative of the gender-based prevalence of the IC in the general population. Meanwhile, due to the very low number of male patients enrolled in the clinical trials, the RMP had been updated to add “use in male patient” as missing information in the summary of safety concerns table in order to collect safety data in men in post-marketing.

Existing post-marketing experience and Nickel *et* al. (2005) data indicate that most common reported AEs were diarrhoea, rectal bleeding and abdominal pain. However a causal relationship between PPS and GIT-AEs is not obvious as GITs are equally reported as associated with the underlying disease and independent of any treatment. In case of a causal relationship, most likely local irritant properties might be responsible regarding an interaction of PPS and mucus the addition to the SmPC to stop the treatment in case of AE and in case of non-efficiency after 6 month of therapy takes this into account.

As limited information is available on use in patients concomitantly using anticoagulants, undergoing invasive procedures or in patients with increased risk of bleeding, a warning statement was included into the SmPC to evaluate these patients carefully for haemorrhage when taking elmiron.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
GRA	Global response assessment (patients reporting at least 6 moderately improved or 7 markedly improved on 7 point numerical rating scale)	Benefit difference (%)	12.4% [IC 95% (6.4-18.3)]	placebo	Inconsistent efficacy : . the main part of the clinical effect is concentrated on old and relatively studies performed with old methodological criteria . Low bioavailability of PPS (< 1%) according to PK data	Primary meta-analysis (ITT) conducted by the Applicant All the 6 pivotal studies

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
GRA	Overall Global response assessment (patients reporting at least 6 moderately improved or 7 markedly improved on 7 point numerical rating scale)	Benefit difference (%)	17%[IC 95% (9.3-24.7)]	placebo	The results are based on studies with old methodological standards. Furthermore 2 studies (Holm-Bentzen et al 1987 and Nickel et al 2015) enrolling a different patient population with the lower response rates are excluded. The Nickel et al study is the most recent and largest trial with an up-to-date methodology but presented several biases (patients with milder IC entering during a symptom flare, regression to the mean, introduction of conservative therapy and failure of clinical sites to keep patients in the trial) .	Sensitivity analysis (ITT) conducted by the Applicant - Parsons and Mulholland (1987) - Mulholland et al (1990) - Parsons et al (1993) - Sant et al (2003)
Pain	RA (50% improvement per symptom)	%	~44 %	Placebo : ~15-18	Pain is improved in only 3 pivotal studies	- Parsons and Mulholland 1987 - Mulholland et al 1990 - Parsons et al 1993
Pain	Responder rates per treatment arm (six pivotal studies)	%	36.7% IC 95% (31.4-42.3%)	Pbo : 21.4 % (11.6-36.2 %)	This result is mainly driven by the 3 pivotal studies with significant results	Six pivotal studies

Unfavourable Effects						
Hair-thinning/ hair loss/alopecia	Known adverse events associated with heparin treatment. Alopecia cited as reversible in the literature.	Frequency (%)	Alopecia: 3.9 (Hanno et al.) to 5% (Nickel et al.) Hair-thinning/ hair loss: 11 % (Waters et al.)		Known adverse events associated with heparin treatment. Causal relationship with PPS highly plausible (heparin-like structure).	Hanno et al. (1997) Nickel et al. (2015) Waters et al. (2000)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence		References
Gastro-intestinal disorders	Diarrhea, abdominal cramping, nausea, dyspepsia.	Frequency (%)	Diarrhea: 2.7% (Parsons et al.) to 15% (Waters et al.) Nausea: 2% (Mulholland et al.) to 9.8% (Nickel et al.) Abdominal cramping : 7% (Nickel et al.) Dyspepsia: 2 (Hanno et al.) to 4% (Nickel et al.)	Diarrhea: 2.7% (Parsons et al.), 5.9% (Nickel et al.) Nausea : 0% (Mulholland et al.) to 7.6% (Nickel et al.)	Gastro-intestinal disorders could be due to the glycosaminoglycan structure of PPS, causing poor tolerance by the gastro-intestinal tract.		Waters et al. (2000) Mulholland et al. (1990) Nickel et al. (2015) Nickel et al. (2005) Parsons et al. (1993) Hanno et al. (1997)
Headache	Headache	Frequency (%)	2% (Mulholland et al.) to 11.5% (Nickel et al.)	3.6% (Mulholland et al.)	Non-specific adverse event. Causal relationship with PPS unknown.		Mulholland et al. (1990) Nickel et al. (2015)
Rectal bleeding	Rectal bleeding	Frequency (%)	4% (Nickel et al.)	No information available	Causal relationship with PPS highly plausible (heparin-like structure).		Nickel et al. (2005)
Bleedings	- epidural hematoma - neck - hematoma -hematomas	%	N/A	N/A	(+): consistent (+/-): relevance to strong menstrual bleeding, rectal bleeding; AE, not clear ADRs		Siddiqui et al.2001 Gill et al 2002 Strohmaier et al. 1987

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Considering the meta-analysis of the four pivotal studies performed with patients falling within ESSIC BPS classification 2X to 3C showed a benefit difference of 17% (PPS versus placebo) and the pooled response rate under PPS treatment even 2-fold higher than the pooled response rate under placebo ("GRA" primary endpoint and also pain and urgency) and following the ad hoc expert group and in the context of unmet medical need (no drug treatment authorized in this indication) the CHMP considers this response rate as clinically relevant in the target population in which efficacy was significantly demonstrated in the pivotal trials and defined with a bladder pain syndrome characterized by either glomerulations of Hunner's lesions and with moderate to severe pain, urgency and frequency of micturition. Also it was essential to define a target population which benefits most from the drug.

The safety of elmiron is not of particular concern. Due to the heparin-like structure of PPS, a weak anticoagulant effect might be observed with elmiron which could become apparent in patients with risk factors for increased bleeding and in patients who actively bleed. This potential risk is considered appropriatly addressed by routine risk minimisation measures.

3.7.2. Balance of benefits and risks

Patients diagnosed with bladder pain syndrome characterized by either glomerulations or Hunner's lesions using traditional diagnostic approach including cystoscopic examination with or without hydrodistension correspond to the population included in four of the six pivotal studies.

Indeed in these four pivotal studies patients reported a better subjective improvement under treatment with pentosan polysulfate sodium compared to placebo. In three of these studies (Parsons and Mulholland 1987, Mulholland et al 1990, Parsons et al 1993), and in contrast to efficacy results in the pivotal studies including a broader BPS population, the observed difference reached statistical significance.
The pooled analysis showed that the percentage of patients responding to treatment with PPS with a clinically relevant improvement in their overall assessment, pain and urgency was approximately 2-fold higher than the respective responder rates under placebo:

	PPS	Placebo
GRA (95% CI)	33,0% (27.1% - 39.4%)	15.8% (11.6% - 21.2%)
Pain (95% CI)	32.7% (26.0% - 40.3%)	14.2% (9.6% - 20.6%)
Urgency (95% CI)	27.4% (21.1% - 34.8%)	14.2% (9.6% - 20.6%)

Furthermore, there are no pharmaceutical treatment alternatives. Indeed, no drug treatment is currently authorized in this indication in Europe. The relatively benign safety profile is considered appropriately addressed by routine risk minimization measures.

The term BPS rather than interstitial cystitis (IC) was put forward by the International Society for the Study of BPS (ESSIC) and is currently used in the guidelines and by the experts.

Overall, the balance of benefit risks of PPS is positive in bladder pain syndrome characterized by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition.

3.8. Conclusions

The overall B/R of elmiron is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of elmiron is favourable in the following indication:

elmiron is indicated for the treatment of bladder pain syndrome characterized by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition (see section 4.4).
The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.