ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

elmiron 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of pentosan polysulfate sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
White opaque capsules size 2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Posology

Adults
The recommended dose of pentosan polysulfate sodium is 300 mg/day taken as one 100 mg capsule orally three times daily.
Response to treatment with pentosan polysulfate sodium should be reassessed every 6 months. In case no improvement is reached 6 months after treatment initiation, treatment with pentosan polysulfate sodium should be stopped. In responders pentosan polysulfate sodium treatment should be continued chronically as long as the response is maintained.

Special populations
Pentosan polysulfate sodium has not been specifically studied in special patient populations like elderly or patients with renal or hepatic impairment (see section 4.4). No dose adjustment is recommended for these patients.

Paediatric population
The safety and efficacy of pentosan polysulfate sodium in children and adolescent below 18 years has not been established.
No data are available.

Method of administration

The capsules should be taken with water at least 1 hour before meals or 2 hours after meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Due to the weak anticoagulant effect of pentosan polysulfate sodium, elmiron must not be used in patients who actively bleed. Menstruation is no contraindication.

4.4 Special warnings and precautions for use

Bladder pain syndrome is a diagnosis of exclusion and other urologic disorders should be eliminated by the prescriber, such as urinary tract infection or bladder cancer.

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 (see section 4.5)) 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.

Hepatic or renal insufficiency
elmiron 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 sodium, hepatic or renal impairment may have an impact on the pharmacokinetics of pentosan polysulfate sodium. Patients with relevant hepatic or renal insufficiency should be carefully monitored when treated with pentosan polysulfate sodium.

Rare cases of pigmentary maculopathy have been reported with use of pentosan polysulfate sodium (PPS), especially after long term use. Visual symptoms might include complaints of difficulty when reading, visual distortions, altered colour vision and/or slow adjustment to low or reduced light environments.
All patients should have an ophthalmologic examination after 6 months of use of PPS for early detection of pigmentary maculopathy, and, if there are no pathologic findings, regularly after 5 years of use (or earlier, in case of visual complaints). However, in case of relevant ophthalmologic findings, a yearly examination should be conducted. In such situations, treatment cessation should be considered.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

A study in healthy subjects revealed no pharmacokinetic or pharmacodynamic interactions between therapeutic doses of warfarin and pentosan polysulfate sodium. No further interaction studies have been performed.

Due to the weak anticoagulant effect of pentosan polysulfate sodium, patients, who are concomitantly treated with anticoagulants, heparin derivatives, thrombolytic or antiplatelet agents including acetylsalicylic acid, or nonsteroidal anti-inflammatory medicinal products should be evaluated for any haemorrhagic event in order to adapt the dose if needed (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of pentosan polysulfate sodium in pregnant women. Animal studies with respect to reproductive toxicity were not conducted.

elmiron is not recommended during pregnancy.

Breast-feeding

It is unknown whether pentosan polysulfate sodium or metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

Therefore, pentosan polysulfate sodium should not be used during breast-feeding.

Fertility
No information on a potential impact of pentosan polysulfate sodium on fertility is available.

4.7 Effects on ability to drive and use machines

Pentosan polysulfate sodium has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The following section lists adverse events reported in the literature from clinical studies with pentosan polysulfate sodium. The potential relatedness between these adverse events and the treatment with pentosan polysulfate sodium was not discussed in the respective publications.

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.

The adverse events reported under treatment with pentosan polysulfate sodium were comparable to those reported under treatment with placebo in regards to quality and quantity.

Tabulated summary of adverse events
Adverse events are listed below by MedDRA body system organ class and by frequency. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data).

Infections and infestations	Common	Infections, influenza
Blood and lymphatic system disorders	Uncommon	Anaemia, ecchymosis, haemorrhage, leukopenia, thrombocytopenia
	Not known	Coagulation disorders
Immune system disorder	Uncommon	Photosensitivity
	Not known	Allergic reactions
Metabolism and nutrition disorders	Uncommon	Anorexia, weight gain, weight loss
Psychiatric disorders	Uncommon	Severe Emotional Lability/Depression
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Increased sweating, insomnia, hyperkinesia, paraesthesia
Eye disorders	Uncommon	Lacrimation, amblyopia
Ear disorders	Uncommon	Tinnitus
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Common	Nausea, diarrhoea, dyspepsia, abdominal pain, abdomen enlarged, rectal haemorrhage
	Uncommon	Indigestion, vomiting, mouth ulcer, flatulence, constipation
Skin and subcutaneous tissue disorders	Common	Peripheral oedema, alopecia
	Uncommon	Rash, increased mole size

Musculoskeletal and connective tissue disorders	Common	Back pain
	Uncommon	Myalgia, Arthralgia
Renal and urinary disorders	Common	Urinary frequency
General disorders and administration site conditions	Common	Asthenia, pelvic pain
Investigation	Not known	Liver function abnormalities

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the case of an accidental overdose, patients should be evaluated for potential adverse effects of pentosan polysulfate sodium like gastrointestinal symptoms or bleeding. In case of adverse reactions, treatment might be paused until the symptoms abate and treatment should be continued at the recommended dose after a critical balancing of the risks thereafter.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, other urologicals, ATC code: G04BX15.

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 reduces bacterial adherence to the inner surface of the bladder 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.

Clinical efficacy and safety
A total of four randomised placebo-controlled, double-blind clinical studies prospectively enrolling patients with bladder pain syndrome diagnosed via cystoscopic examination with or without bladder hydrodistension evaluating the efficacy of oral treatment with pentosan polysulfate sodium were published in scientific literature. In all of these studies, patients reported a better subjective improvement of bladder pain syndrome under treatment with pentosan polysulfate sodium compared to placebo. In three studies, the observed difference was clearly statistically significant.
The first study was a double-blind, randomized, placebo-controlled study with a planned cross-over design evaluating pentosan polysulfate sodium versus placebo. Depending on which institution the patients attended they were treated with either 3x100 mg or 2x200 mg PPS per day. 75 patients were randomised into the study and 62 of those completed the study. Efficacy of treatment was evaluated based on the patient reported improvement on four typical symptoms of bladder pain syndrome: pain, urgency, frequency, and nocturia, no primary endpoint was defined. A patient was counted as a responder to treatment in case a 50% improvement compared to baseline was reported for a specific symptom after 3 months of treatment. An evaluation of all data generated in the study showed that for all four symptoms statistically significant more patients responded to pentosan polysulfate sodium treatment compared to placebo:

	PPS	Placebo	P-value
Pain			
No. responders / total (%)	19/42 (45)	7/38 (18)	0.02
Av. % improvement*	33.0 ± 35	15.8 ± 26	0.01
Urgency			
No. responders / total (%)	21/42 (50)	9/48 (19)	0.03
Av. % improvement*	27.6 ± 31	14.0 ± 24	0.01
Frequency			
No. responders / total (%)	33/52 (63)	16/41 (39)	0.005
Av. improvement	-5.1	-0.4	0.002
Nocturia			
Av. improvement*	-1.5 ± 2.9	-0.5 ± 0.5	0.04

(*Mean ± SD)

The following two studies were conducted following very comparable double-blind, randomized, placebo-controlled multicentre study designs. The patients in both studies were treated for three months with either 3x100 mg pentosan polysulfate sodium or placebo. The primary efficacy endpoint of the study was the overall improvement as self-reported by the patient after three months of treatment. The patients were asked whether they felt improved overall since the start of treatment, and if so, whether the improvement was “slight” 25%, “moderate “50%, “great” 75% or “complete cure” 100%. Patients who reported at least moderate (50%) improvement were counted as responders. The secondary efficacy endpoints included the investigators evaluation of improvement. The used scale for the investigators assessment included the categories “worse”, “no change”, “fair”, “good”, “very good”, and “excellent”. A responder was defined as a patient assessed to be at least “good” compared to baseline. Furthermore volume voiding profiles over three days and the impact of treatment on pain and urgency were evaluated as secondary endpoints. The impact on pain and urgency was evaluated via the same questionnaire as the primary endpoint with a responder defined as a patient experiencing an at least moderate (50%) improvement compared to baseline. In addition the impact on pain and urgency was evaluated via a 5 score scale, where a responder was defined as a patient experiencing at least a 1-point improvement compared to baseline.
110 patients were enrolled and treated for three months in the first of the two very comparable studies. A statistically significant benefit of pentosan polysulfate sodium over placebo was demonstrated over the primary endpoint, the patients overall-assessment of improvement as well as on the investigators overall assessment. Furthermore a trend for better efficacy of pentosan polysulfate sodium was observed for the patients self-assessment of an improvement of pain and urgency, despite a deviating effect observed for the evaluation of urgency via the scale. In addition positive effects were observed on the voiding profile, although the observed differences were not statistically significant:

	PPS	Placebo	P-value
Responders based on patients self-evaluation of overall improvement	28%	13%	0.04
Responders based on investigators evaluation of overall improvement	26%	11%	0.03
Responders regarding pain and urgency			
Pain (moderate/50% improvement)	27%	14%	0.08
Pain scale (1-point improvement)	46%	29%	0.07
Pressure to urinate (moderate/50% improvement)	22%	11%	0.08
Urgency scale (1-point improvement)	39%	46%	ns
Mean reduction in pain score from baseline	0.5	0.2	ns
Changes from baseline voiding characteristics			
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
Voids per day	-1	-1	ns
3 voids less per day (% pts)	32	24	ns
Nocturia	-0.8	-0.5	ns

The second of the two very comparable studies enrolled 148 patients and demonstrated a statistically significant benefit pentosan polysulfate sodium over placebo was demonstrated on the patient reported overall improvement evaluated as primary endpoint and an the investigator-assessed overall improvement, all evaluations on pain and urgency. A trend for better efficacy under pentosan polysulfate sodium was observed for improved sexual intercourse:

	PPS	**Placebo**	**P-value**
Responders based on patients self-evaluation of overall improvement	32%	16%	0.01
Responders based on investigators evaluation of overall improvement	36%	15%	0.002
Responders regarding pain and urgency			
Pain (moderate/50% improvement)	38%	18%	0.005
Pain scale (1-point improvement)	66%	51%	0.04
Pressure to urinate (moderate/50% improvement)	30%	18%	0.04
Responders regarding pain and urgency	61%	43%	0.01
Improved sexual intercourse	31%	18%	0.06
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

The fourth study was following a double-blind, double-dummy, multifactorial design and evaluated the effects of pentosan polysulfate sodium and hydroxyzine in one study. Patients were randomized to four treatment group and were treated for six months with 3x100 mg pentosan polysulfate sodium, 1x50 mg hydroxyzine, both active treatments, or placebo. A responder analysis based on a patient-reported Global Response Assessment (GRA) after 24 weeks of treatment was defined as primary endpoint. The GRA assessment was evaluated via a 7-point centred scale, in which the patients can assess their global response compared to baseline as markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved or markedly improved. Participants who reported either of the latter two categories were defined as treatment responders. 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. Comparison of those patients receiving pentosan polysulfate sodium with those not receiving pentosan polysulfate sodium (irrespective of treatment with oral hydroxyzine) revealed no statistically significant difference between the two group, but a trend for better efficacy was observed for the primary endpoint in those patients treated with pentosan polysulfate sodium (either alone or in combination with hydroxyzine) (20 of 59, 34%) compared to the those patients not receiving pentosan polysulfate sodium, but who might receive hydroxyzine (11 of 62, 18%, p0.064):

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

A pooled analysis of the data described above from placebo-controlled clinical studies was conducted to evaluate, whether patients taking oral pentosan polysulfate sodium have clear benefit from the treatment. This pooled analysis showed that the percentage of patients responding to treatment with pentosan polysulfate sodium 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%)

5.2 Pharmacokinetic properties

Absorption
Less than 10% of orally administered pentosan polysulfate sodium are slowly absorbed from the gastrointestinal tract and are available in systemic circulation in the form of unchanged pentosan polysulfate sodium or it's metabolites. All studies describe very low systemic availability of unchanged pentosan polysulfate sodium after oral administration. Overall, the reported systemic bioavailability after oral administration of pentosan polysulfate sodium is below 1%.

Distribution
In healthy volunteers, a single parenteral administration of radioactively labelled pentosan polysulfate sodium leads to a progressive up-take of total radioactivity by the liver, spleen, and kidney (50 min after 1 mg/kg i.v.: 60 % of the dose in the liver, 7.7 % in the spleen; 3 h post dosing: 60 % in the liver plus spleen, and 13 % in the bladder).

Biotransformation
Pentosan polysulfate sodium is metabolised extensively by desulfation in liver and spleen and depolymerisation in the kidney.

Elimination
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. Accordingly, 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). After oral administration unabsorbed pentosan polysulfate sodium is excreted predominantly unchanged in the faeces. About 6% of the administered dose of pentosan polysulfate sodium were excreted via urine after desulfation and depolymerisation.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional repeated dose toxicity, genotoxicity and long-term carcinogenicity studies.
The effect of pentosan polysulfate sodium on reproductive and developmental toxicity has not been investigated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Microcrystalline cellulose
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottle
3 years
After first opening: use within 45 days.

Blister
21 months

6.4 Special precautions for storage

Bottle
Keep the bottle tightly closed in order to protect from moisture.
For storage conditions after first opening of the bottle, see section 6.3.

Blister
Do not store above 30 °C.

6.5 Nature and contents of container

HDPE bottle with a tamper-evident child resistant closure of PP with 90 capsules.
HDPE bottle with a tamper-evident child resistant closure of PP with 100 capsules.

PVC/Aclar-Aluminium blister with 90 (9x10) capsules.

Bottle
Pack size of 90 capsules.
Pack size of 300 (3 bottles x 100) capsules.

Blister
Pack size of 90 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1189/001
EU/1/17/1189/002

EU/1/17/1189/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 June 2017

10. DATE OF REVISION OF THE TEXT

31.08.2020

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu