Position Statement: Pentosan Polysulfate Sodium (PPS) and Pigmentary Maculopathy (PM)

EXECUTIVE SUMMARY

Paradigm Biopharmaceuticals Ltd. is developing pentosan polysulfate sodium (PPS; iPPS)—a semisynthetic macromolecular carbohydrate derivative that resembles glycosaminoglycans (GAGs)—for the treatment of pain and function in patients with knee osteoarthritis.

A recent article by Fung et al investigates the development of pigmentary maculopathy in three patients who had received a compounded form of injectable PPS (not Paradigm's product) (Fung et al., 2025 [1]). The exposure details of the three cases compared to Paradigm's program are summarised in Table 1:

Table 1 PPS-associated maculopathy using compounded subcutaneous PPS

	Case 1	Case 2	Case 3	Paradigm's iPPS for OA
PPS manufacturer	unknown	unknown	unknown	bene pharmaChem GmbH
Compounded by	unknown	unknown	unknown	NA
Average dose	125 mg SC twice weekly at 250 mg/mL	3,000 mg SC every 12 weeks at 300 mg/mL	87.5 mg SC weekly at 125 mg/mL	2 mg/kg SC twice weekly for six weeks for an estimated 2–3 cycles, at minimum 6-month intervals
Cumulative dose	91 g	96 g	45.5 g	estimated 4.8–7.2 g
Duration of use	7 years	8 years	10 years	6 weeks per cycle
Country	AU	USA	USA	AU, USA

Abbreviations: AU–Australia; NA–not applicable; SC–subcutaneous; USA–United States of America. Table data from (Fung et al., 2025 [1]) and Paradigm.

The three cases in the Fung et al article were exposed to significantly higher cumulative doses and for longer durations of use when compared to Paradigm's iPPS.

Throughout nine Paradigm-sponsored clinical trials evaluating the pharmacokinetics (PK), safety, and/or efficacy of iPPS, over 600 participants have received iPPS of varying doses and frequencies. For these studies, subcutaneously injected 2 mg/kg PPS twice weekly is the highest dose evaluated, where treatment courses in osteoarthritis studies have not exceeded six weeks. Additionally, more than 700 patients have been treated with iPPS as part of the ongoing TGA Special Access Scheme managed access program in Australia.

Since 2018, scientific literature has suggested that there may be a dose-dependent relationship with long-term oral PPS use and the development of pigmentary maculopathy. As such, and in tandem with guidance from the FDA, Paradigm implemented robust ophthalmic monitoring within the clinical development program to screen for and follow up on any retinal and visual changes in participants from phase 2 studies PARA_OA_008 and PARA_OA_002. In thethe ongoing phase 3 study PARA_OA_012, all participants will undergo baseline and follow-up retinal examination during the last study visit.

There has been no evidence of iPPS-associated maculopathy reports within Paradigm's programs, however, Paradigm continues to closely monitor patient safety. In our clinical trials, patients with pre-existing serious retinal disease are excluded. Furthermore, these studies have and are generating controlled clinical data on the risk of pigmentary maculopathy with iPPS and will form the basis of a future publication.

In conclusion, Paradigm considers the risk of developing pigmentary maculopathy with iPPS within Paradigm's development program to be very low. Paradigm has implemented prospective ophthalmic screening, patient / health professional education, and dose-duration management to mitigate the potential risk while maintaining therapeutic benefit. Paradigm's mitigation strategy aligns with international best practices and will be continuously refined as more data becomes available.

Reference

[1] Fung AT, Sarraf D, Carrillo JM, et al. Pentosan Polysulfate Maculopathy Following Subcutaneous Injections for Arthritis. JAMA Ophthalmol [Internet]. 2025;e255069. doi:10.1001/jamaophthalmol.2025.5069.