MODULE 2.4: NON-CLINICAL OVERVIEW

Product: Poly-Zinc-Liothyronine (PZL)

Active Ingredient: Liothyronine (T3)

Formulation: Sustained-Release Coordination Complex

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1. INTRODUCTION AND STRATEGIC RATIONALE

Liothyronine administered via the oral route leads to an abnormal and sharp pharmacokinetic distribution that dissipates during the next several hours. This differs remarkably from the equivalent profile in healthy subjects. Hence, it is highly suggestive to develop new formulations and strategies for delivering T3(Idrees et al., 2019).

The goal of this program is the development of Poly-Zinc-Liothyronine (PZL), a novel, metal-coordinated polymeric complex designed to provide stable, physiological circulating levels of triiodothyronine (T3). Standard oral liothyronine (LT3) therapy is characterised by rapid absorption and clearance, leading to supra-physiological serum peaks (Cmax) and subsequent rapid declines, which are often associated with adverse cardiovascular events such as tachycardia.

PZL utilises Coordination Chemistry to create a supramolecular structure that adheres to the intestinal mucosal lining, creating a localised depot for sustained systemic absorption. This approach specifically targets patients with impaired T4-to-T3 conversion or gastrointestinal malabsorption issues.

2. PHARMACOLOGY

2.1 Primary Pharmacodynamics

The primary pharmacodynamic activity of PZL is the restoration of euthyroidism through the controlled release of T3.(Celi et al., 2011; Idrees et al., 2019)

- **Mechanism of Action:** PZL is a polymeric coordination complex where T3 acts as a **tridentate ligand**, binding to zinc via amino acid and phenol groups.
- **Controlled Release:** The release of the active hormone occurs through slow **ligand exchange (hydrolysis)** within the gastrointestinal environment,

ensuring the API enters the bloodstream at a rate that mimics natural thyroidal secretion.
- **Efficacy:** Pre-clinical models in hypothyroid rats demonstrate that PZL effectively restores growth and lowers serum cholesterol, matching the therapeutic efficacy of standard LT3 without the associated serum excursions.

2.2 Safety Pharmacology

The sustained-release profile of PZL significantly mitigates the risk of **Thyrotoxicosis-induced cardiotoxicity**.

- Compared to LT3, PZL-derived T3 exhibits a significantly lower Cmax (approximately 30% reduction) and a delayed Tmax.(Idrees et al., 2019)
- Clinical monitoring in healthy volunteers showed no significant deviations in heart rate, blood pressure, or sleep patterns, confirming a favourable safety pharmacology profile.
- Zinc exposure via the release of LT3 via hydrolysis of PZL is 0.045% of the tolerable upper limit (for a normal dose on a male subject). (ICH Q3D(R2))

3. PHARMACOKINETICS

The pharmacokinetic (PK) profile of PZL is the cornerstone of its clinical advantage.

PK Parameter	LT3 (Standard Tablet)	PZL (Coordination Complex)	Regulatory Impact
Tmax	2–3 Hours	4–9 Hours (Delayed)	Reduced acute cardiovascular risk.
Cmax	High peak (sub-toxic)	~30% Lower, Stable plateau	Avoids peaks/valleys of serum levels.
Absorption	Rapid and erratic	Sustained via mucoadhesion	Improved dose predictability.

4. TOXICOLOGY (INTEGRATED ASSESSMENT)

The toxicological assessment of PZL focuses on the safety of the metal-coordinated matrix.

- **Zinc Exposure:** The zinc utilised in the coordination complex is well below the **Permitted Daily Exposure (PDE)** for chronic therapeutic use.(Dumitrescu et al., 2022; ICH Q3D Guideline for Elemental Impurities)
- **Genetic Toxicity:** Given the endogenous nature of the ligand (T3) and the established safety of the metal ion, the risk of mutagenicity is considered negligible.
- **Local Tolerance:** PZL displays high mucosal tolerance due to its supramolecular properties, with no evidence of intestinal irritation in chronic dosing models.(Da Conceição et al., 2018)

5. OVERALL CONCLUSION

Non-clinical data for PZL demonstrate a superior pharmacokinetic and safety profile compared to current market standards. By utilising **Inorganic Coordination Chemistry**, this product successfully addresses the pharmacological shortcomings of liothyronine therapy, supporting its progression into late-phase clinical evaluation for the management of hypothyroidism.