

SmPC and PI Alignment Brief

Product Name: Cardiolase (ivabradine hydrochloride)

Markets: EU (SmPC v5.1), Japan (PI v3.0)

Prepared by: Regulatory Affairs - Labelling

1. Objective

Identify language differences between EU SmPC and Japan PI that may introduce medical, legal, or promotional risk. Focus areas include indications, contraindications, special warnings, and patient instructions.

2. Summary of Findings

2.1 Indications

- EU SmPC: "Adult patients with chronic heart failure with reduced ejection fraction who are in sinus rhythm and have a heart rate ≥ 75 bpm."
- Japan PI: "Adult patients with chronic heart failure (NYHA Class II to IV) who are in sinus rhythm and have a heart rate ≥ 70 bpm."

Review Point 1: Confirm local clinical justification for the broader NYHA range in PI Section 1. Align with risk management plan addendum.

2.2 Contraindications

- SmPC Section 4.3 includes hypersensitivity to excipients; PI omits explicit mention of polysorbate 80.
- PI uniquely adds "history of severe hepatic impairment" not present in SmPC.

2.3 Special Warnings and Precautions

- SmPC Section 4.4 warns against concomitant use with strong CYP3A4 inhibitors such as ketoconazole; PI lists only macrolide antibiotics.
- PI includes additional cautionary language for patients receiving dialysis.

Review Point 2: Evaluate whether dialysis caution should be added to SmPC or justified as Japan-specific based on post-marketing surveillance.

3. Dosing and Administration

Population	SmPC	PI
Starting dose	5 mg twice daily	5 mg twice daily
Titration	Increase to 7.5 mg based on heart rate	Increase to 7.5 mg after 2 weeks if HR ≥ 75 bpm
Pediatric use	Not recommended	Not indicated

4. Patient Instructions

- SmPC patient leaflet references "blurred vision when driving at night"; PI translation states "temporary brightness" without driving guidance.
- PI patient instructions include an additional section on adherence to salt restriction.

5. Packaging and Storage Statements

Both documents specify storage below 25 degC and protection from light. PI adds requirement to dispense with child-resistant closures.

6. Next Steps

1. Convene labelling alignment meeting with EU and Japan medical leads by May 15, 2026.
2. Draft SmPC variation proposal including dialysis caution if evidence supports inclusion.
3. Update PI translation glossary to standardize visual disturbance language.

7. Appendices

- Appendix A: Side-by-side comparison table (detailed).
- Appendix B: Post-marketing safety data excerpts supporting dialysis caution.

8. Approvals (Draft)

- RA Director EU: _____
- RA Director JP: _____
- Medical Affairs Lead: _____