Contents

Chapter 1 General introduction and thesis outline 9

Chapter 2 Pharmaceutical and clinical development of phosphonate-based radiopharmaceuticals for the targeted treatment of bone metastases Bone 2016;91:159-179. 23

Chapter 3 Untangling the web of European regulations for the preparation of unlicensed radiopharmaceuticals: a concise overview and practical guidance for a risk-based approach Nuclear Medicine Communications 2015;36:414-422. 99

Chapter 4 Bench to bedside development of GMP-grade rhenium-188-HEDP, a radiopharmaceutical for targeted treatment of painful bone metastases International Journal of Pharmaceutics 2014;465:317-324. 117

Chapter 5 Drug composition matters: the influence of carrier concentration on the radiochemical purity, hydroxyapatite affinity and in vivo bone accumulation of the therapeutic radiopharmaceutical $^{188}\text{Re}$rhenium-HEDP Nuclear Medicine and Biology 2015;42:465-469. 137

Chapter 6 Applying quality by design principles to the small-scale preparation of the bone-targeting therapeutic radiopharmaceutical rhenium-188-HEDP European Journal of Pharmaceutical Sciences 2016;90:96-101. 149

Chapter 7 Cytotoxic effects of the therapeutic radionuclide rhenium-188 combined with taxanes in human prostate carcinoma cell lines Submitted 163
Chapter 8  Treatment of painful bone metastases in prostate and breast cancer patients with the therapeutic radiopharmaceutical rhenium-188-HEDP – Clinical benefit in a real-world study  
_Nuklearmedizin/NuclearMedicine 2016;55(5):188-195._

Chapter 9  General summary, discussion and future perspectives  
_Samenvatting, discussie en toekomstperspectieven_

Chapter 10  Dankwoord (Acknowledgements)  
_Curriculum vitae_  
_Biography_  
_List of publications_  
_Rhenium fact sheet_