radionuclide therapy. Occasional indications also exist for use of SSAs pre systemic chemotherapy if the functional symptoms are extreme. Short acting octreotide is still used for breakthrough functional symptoms and around the time of surgical intervention or PRRT, given either as intermittent subcutaneous doses or via intravenous infusion.

The anti-proliferative activity of SSAs has been shown in randomized trials with both octreotide and lanreotide. The details of the PROMID and CLARINET studies are covered in Chapter 8: Systemic therapies: Somatostatin analogues and targeted agents.

A common question arising in clinical practice is the interplay between timing of long acting SSAs and 68Ga-DOTATATE PET. While the early Guidelines *[218]* recommend withholding long acting SSA therapy for at least 4 weeks prior to somatostatin receptor scintigraphy, the scan can be performed sooner as long as the interpreter is aware of the potential altered biodistribution, commonly a decrease in physiological uptake in the thyroid, liver and spleen and potentially an increase in tumour uptake *[107][108]*. The more recent EANM Guidelines state that "There is no clear evidence that discontinuation of somatostatin analogues prior to PET imaging with 68Ga-DOTA-conjugated peptides is necessary" *[72]*. Patients who are intolerant of an interruption of SSA therapy may be managed with short acting agents, which can be ceased close to the time of the scan.

7.3 Functional Syndrome (Carcinoid Syndrome)

Carcinoid syndrome is a term that describes the constellation of symptoms related to various hormones secreted by some NENs *[225]*. Most common symptoms include flushing, diarrhoea and bronchoconstriction. The majority of patients with carcinoid syndrome have metastatic disease typically to the liver which secretes hormones directly into the systemic circulation. The most important hormone implicated in causing these symptoms, especially diarrhoea is serotonin. The enzyme tryptophan hydroxylase is an important rate limiting step in the conversion of the amino acid tryptophan to serotonin.

Standard SSA is first line therapy as noted for functional syndromes. An oral tryptophan hydroxylase inhibitor (Telotristat ethyl) was developed to help control diarrhoea associated with carcinoid syndrome in conjunction with SSA therapy for patients failing standard therapy. The FDA approval in 2017 was based on the results of the TELESTAR Trial where treatment with telotristat was associated with a statistically significant reduction in the frequency of bowel movement over time compared to placebo *[226]*. Telotristat was approved by the TGA in September 2018 but is not as yet subsidized by the PBS in Australia.

7.4 Carcinoid Crisis

Carcinoid crisis is a life threatening form of carcinoid syndrome which typically presents as wide blood pressure fluctuations with a predominance of hypotension. This is secondary to the release of large amounts of biologically active substances that could be the results of tumour manipulation (biopsy or during surgery) or by anaesthesia. Increasingly it is also seen as a result of PRRT or liver directed therapies. Symptoms are generally resistant to fluid resuscitation alone *[227][228][229]*. Management of hypotension can be with an octreotide infusion (500 to 1000 mcg intravenously; a continuous intravenous drip of octreotide at a rate of 50 to 200 mcg/hour may also be used) *[227][230]*.

7.5 Carcinoid Heart Disease

Carcinoid heart disease occurs in 20-50% of patients with carcinoid syndrome *[231][232]*. Chronic exposure to high concentration of circulating serotonin is thought to be a major factor in the development of carcinoid heart disease. Usually it is characterized by plaque like fibrous endocardial thickening that involves the right side of the heart and often leads to retraction and fixation of the leaflets of the tricuspid and pulmonary valves.