Pharmacotherapeutic report, summary

Pasireotide (Signifor®) for the indication 'Cushing's Disease'
Approved on 24-09-2012 by the Medicinal Products Reimbursement Committee (CFH)

Medicine. Pasireotide 0.3, 0.6 or 0.9 mg/ml in a solution for subcutaneous injection.

Registered indication. 'For the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed."

Posology. The recommended initial dose is 0.6 mg via subcutaneous injection, twice daily. The effect of treatment on patients should be assessed two months after starting treatment.
The treatment of patients in whom the concentration of urinary-free cortisol falls considerably should be continued as long as the favourable effect persists. Depending on the response to treatment, increasing the dose up to 0.9 mg twice daily may be considered as long as the twice daily dose of 0.6 mg is well tolerated by the patient. Terminating the treatment should be considered for patients who have not responded to the treatment after two months. A temporary dose reduction may be necessary if side effects of treatment are suspected during treatment. Stepped reductions of 0.3 mg twice daily are recommended.

Mechanism of action. Pasireotide is a somatostatin analogue which exerts its pharmacological effect via binding to somatostatin receptors. There are five known human somatostatin receptor (hsst) subtypes known to man, i.e., hsst1, 2, 3, 4 and 5. Pasireotide is bound to, and activates, four of the five hsst subtypes, particularly hsst5, which results in inhibition of the ACTH secretion.

Specific details. Pasireotide is registered as an orphan drug.

Summary of the therapeutic value

Intended effects. In a phase III study involving patients with Cushing's disease, after six months' treatment the percentage of responders was 15% in the pasireotide 600 µg bid arm and 26% (95% BI: 17-37%) in the pasireotide 900 µg bid arm. The average absolute change in the concentration of urinary-free cortisol in comparison with the starting value was -463 nmol/24 hours in the pasireotide 600 µg bid arm and -365 nmol/24 hours in the pasireotide 900 µg bid arm. In total, 25% of the patients stopped treatment within 12 months due to insufficient efficacy. In view of the short follow-up time of the most important study, the long-term favourable effects of pasireotide are still unknown.
In the Netherlands, current clinical practice is to use metyrapon, ketoconazol (off-label) or cabergoline (off-label) for patients with Cushing's Disease. The favourable effects of these three products was determined in a few small, retrospective studies of patients with Cushing's Disease for whom operation is impossible or was unsuccessful. Based on the results of these studies, there are only indications that these drugs are effective. No firm conclusions can be drawn from the indirect comparisons made due to differences in study set-up, definition of the (primary) endpoint, duration of treatment and the patients studied.

Unintended effects. The most frequent adverse effects (>20%) that occurred during treatment with pasireotide were diarrhoea, nausea, hyperglycaemia, the presence of gall stones and stomach ache. In general most side effects are mild to moderate. The percentage of patients with severe treatment-related adverse effects was 13% (600 µg bid arm = 9% and 900 µg bid arm = 15%). The most frequently reported severe adverse effects were the presence of gall stones and events relating to hyperglycaemia. In the phase II study 28 patients (17%) stopped treatment due to side effects. Furthermore, a dose adjustment or temporary interruption in treatment was necessary in 55 patients (34%). The long-term side effects of pasireotide are still unknown.
A comparison between the adverse effects of pasireotide and those of treatments with which it was compared was hampered by the limited data on the adverse effects of the comparative treatments for patients with Cushing's Disease.
Experience. Experience with pasireotide is limited, while ample experience has been gained with the comparative treatments because these drugs have been on the market for more than 10 years.
Applicability. Pasireotide has no specific advantages in applicability. Differences in applicability are insufficient to warrant a decisive preference.
Ease of use. Patients administer pasireotide themselves, twice daily subcutaneously. Other treatments are given orally, but with the disadvantage of a large number of tablets per day.
Final conclusion. In a phase II clinical study, treatment with pasireotide resulted in an increase in the percentage of patients with a normalised concentration of urinary-free cortisol (responders). The response percentage was, however, low. In comparison with pasireotide, data on the efficacy and safety of ketoconazol, cabergoline and metyrapon in adult patients for whom surgery is not an option or for whom surgery has failed is extremely limited and comes from small, retrospective studies. The results of these studies indicate only that these drugs are effective and safe in patients from whom surgery is not an option or for whom surgery has failed. No firm conclusions can be drawn from the indirect comparisons in view of the differences in study set-up, treatment duration, definition of outcome measures and the patients studied.
Partly due to the poor prognosis and the current limited treatment possibilities for this orphan indication, pasireotide has an added therapeutic value, despite the low response percentage, in comparison with ketoconazol, cabergoline and metyrapon, in the treatment of adult patients with Cushing's Disease for whom surgery is not an option or for whom surgery has failed.

*The original text of this excerpt from a **CFH-Report** of CVZ was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of CVZ's CFH-Report.*
Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.