Clinician and Patient Involvement Group (CAPIG) Meeting Summary Pasireotide (as pamoate) (Signifor®▼) 20 mg, 40 mg, 60 mg powder and solvent for suspension for injection

Marketing authorisation holder

Novartis Pharmaceuticals UK Ltd.

Licensed indication

Pasireotide (as pamoate) (Signifor®▼) for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue.

Company's proposed positioning (if any)

In accordance with the licensed indication.

1. Severity of the condition

Acromegaly is a rare, incurable, progressive disorder that has an extensive impact on the patients' physical, mental and emotional health. Not only are symptoms disabling but they are also disfiguring, and as a result, the impact on patients' quality of life is considerable. Patients with acromegaly suffer with significant changes in physical appearance as well as multiple co-morbidity conditions. Diagnosis is often delayed by several years, which is traumatic for patients and their families, as the non-specific symptoms mean the true root of disease (pituitary adenoma) can be missed, and patients are managed for other conditions instead. Patients have a mortality rate that is approximately twice that of the general population, and an average reduction in life expectancy of ten years.

While many patients with acromegaly are treated through surgery and radiotherapy successfully, for some patients their disease remains uncontrolled. These patients have the "*worst*" acromegaly: they are highly symptomatic, seriously unwell, and at risk of increased mortality. Symptoms are wide-ranging and include fatigue, joint aches, lack of libido, erectile dysfunction in men, excess growth which can affect internal organs, enlarged lips, nose, feet, hands and tongue, plus protruding lower jaw and brow, excessive sweating, abnormalities of the menstrual cycle, headaches, vision disturbance, high blood pressure and sleep apnoea. Patients may require surgery to address symptoms such as excess growth: for example, a patient may need their jaw broken and realigned to allow for their teeth to meet. Equally for these patients, a major concern is that of co-morbidities; these include bowel cancer, hypertension, diabetes mellitus, valvular heart disease and cardiac dysrhythmia/arrhythmia. These are serious health and quality of life issues for patients living with uncontrolled acromegaly.

Patients struggle to maintain their daily routines or social activities, and many are unable to work or study, or continually need to take time off. Patients report extreme fatigue as having one of the biggest impacts on their daily lives. They find it difficult to sleep because of pain and often only sleep a few hours at a time. Many spend most of their day drifting in and out of sleep, being unable to concentrate or follow instructions, and find it difficult to remember things. Many report a loss of independence and some patients struggle to walk or drive because of joint pain, and are only able to leave the house to attend essential hospital appointments or surgery. Patients feel frustrated because they want to be more active but find it impossible to do so.

A social life becomes impossible and relationships strained due to the severity of the symptoms. Comments about the physical changes that patients experience, particularly those to facial features, skin, and weight, can be hard to accept and instill a lack of

confidence. Patients often feel anxious and uncomfortable in social situations, resulting in social avoidance, isolation and a feeling of alienation.

2. Unmet need

Approximately 95% of patients with acromegaly would undergo transsphenoidal pituitary surgery as the initial treatment, of which about 70% would be expected to achieve biochemical cure. The other 5% of patients would not undergo surgery either because the risk is considered too great or because a patient does not wish to consider this option.

In the 30% of patients not cured by surgery, and for the 5% who have not undergone surgery at all, a somatostatin analogue (octreotide long-acting release [LAR] or lanreotide autogel) may then be considered. A dopamine agonist (cabergoline) alone or in combination with a somatostatin analogue may be considered for a small number of patients (approximately 10%) with co-existing hyperprolactinaemia or "*mild*" biochemical excess. For those patients treated with medical therapy, adequate biochemical control would be expected in 70% (stated to be greater for somatostatin analogue than dopamine agonist). Patients with inadequately controlled disease at this stage may switch from octreotide to lanreotide, or vice versa, if they are intolerant of one preparation or in an attempt to gain control but this is only considered in a very small number of our patients.

For the residual patients, the treatment option would be radiotherapy, in the absence of availability of pegvisomant in Wales. About 60% of patients would normalise biochemistry following radiotherapy (stereotactic or conventional), but this often takes many years; therefore, medical therapy may need to continue until this is achieved. The clinical expert stated that, in their opinion, it would be this small group of patients where pasireotide (or pegvisomant if available) would be considered. Even in this group, clinicians would usually distinguish between "*mild*" growth hormone excess (slightly raised insulin-like growth factor-1 [IGF-1] with few symptoms) where a "*watch and wait*" approach might be followed, and more severe acromegaly which would definitely need treatment. Therefore, the clinical expert estimated that fewer than five patients in Wales would be considered for treatment with pasireotide.

Pasireotide gives hope to those few patients who are unable to control their condition through any other means. Patients describe how distressing it is to receive various other kinds of treatment but see no improvement in their condition or experience worsening of their symptoms. Their symptoms become worse, the pain is debilitating, they feel socially excluded and everyday is a challenge. Patients feel that the introduction of pasireotide would be a transformational and life changing opportunity. Knowing that there is a possibility of new treatment in the future gives patients a reason to return to clinic and feel positive about their future. Clinicians state that there is a definite unmet need for these patients who cause the greatest concern. Pasireotide could benefit these patients considerably.

In this small cohort of patients, pasireotide would offer an effective medical treatment option. Clinical studies have demonstrated that pasireotide can address many of the unmet needs in this cohort. For example, by achieving biochemical control and halting, or even reversing, soft tissue symptoms such as excess growth and enlarged lips, nose, feet, hands and tongue. Pasireotide can also decrease tumour size, thus improving a patient's symptoms such as their visual disturbances and headaches. Furthermore, pasireotide can help improve cardiomyopathy, and enable hypertension or diabetes to be controlled more effectively. The benefits of treatment with pasireotide could translate into a gain in life expectancy.

Not all patients will respond to pasireotide, but for the small number that do, the treatment will provide an option to those who cause the greatest concern. In all patients with uncontrolled acromegaly, clinicians consider that being able to achieve some control in the disease is better than none since it can have an impact on co-morbidities.

CAPIG explored the issue of clinical access and exit criteria. The clinical expert explained the pathway in Wales and confirmed that non-responders to pasireotide can be identified within three months of from the start of therapy. If there was no biochemical shift, then treatment would stop. The clinical expert stated that they personally treat all new patients with acromegaly, and highlighted that there are only three prescribers in Wales. The clinical expert offered to prepare a clinical pathway relevant to Wales highlighting the number of patients likely to be prescribed pasireotide in Wales. The marketing authorisation holder confirmed that they were developing a Treatment Protocol Guidance document relating to the assessment of patients at three months, and offered to share this with AWTTC/AWMSG.

Pasireotide has been approved for use in Scotland by the Scottish Medicines Consortium and a commissioning policy is currently being developed in NHS England. The clinical expert explained that access via the Individual Patient Funding Request (IPFR) process would be unlikely since it is difficult to demonstrate exceptionality due to the nature of the disease. If pasireotide is not recommended for use within NHS Wales then patients living in Wales will be at a disadvantage over patients in the rest of the UK as there will be no route of access to this medicine. CAPIG members considered the inequitable access would be unacceptable.

3. Added value of the medicine for the patient:
3a. How would this medicine be expected to add value to the patient's wellbeing and experience of care?

Patients with uncontrolled acromegaly are very keen for a new medication to be made available. The impact of the condition on a patient's health and quality of life is considerable and pasireotide would provide an option to patients who would otherwise have to continue living with this distressing condition.

Clinical trials have demonstrated that treatment with pasireotide can result in biochemical control and reversal of some of the signs and symptoms of acromegaly, as well as reduction in tumour volume, in patients with uncontrolled acromegaly. Pasireotide can also have a positive impact on co-morbidities and life expectancy.

Improvements in physical symptoms can have significant affects on a patient's psychological wellbeing. Qualitative studies exploring the impact of acromegaly on quality of life and the psychological distress it can cause, have demonstrated that many patients have appearance-related concerns and clinical levels of anxiety or depression. This can result in a shrinking life due to social anxiety and social avoidance, and dissatisfaction with their ability to work and with the quality of their relationships. Pasireotide would provide patients with the opportunity to become active members of their family, the workplace and society once more.

3b. How is this medicine better than current treatments?

Pasireotide is a second-generation somatostatin analogue licensed for use in patients inadequately controlled with another somatostatin analogue. It has a broader somatostatin receptor binding profile than the current predominant therapeutic treatment options (first-generation somatostatin analogues), with high affinity to four of the five receptors.

Other medical treatment options for treating patients inadequately controlled on a somatostatin analogue include pegvisomant (Somavert®). However, pegvisomant has a different mechanism of action to pasireotide, is administered as a daily injection, does not provide a full biochemical control of the disease, does not target the tumour itself or reduce tumour size, and does not reverse soft-tissue symptoms. Furthermore, pegvisomant is not recommended for use within NHS Wales. Pasireotide is administered through a monthly injection, and clinical trials have demonstrated that treatment with pasireotide can provide biochemical control, reduces tumour size and

reverse some of the symptoms. In the absence of effective medical therapies in Wales, pasireotide offers a small group of patients, who are left with significantly impaired quality of life and expected premature death, a potentially life changing opportunity to manage their disease.

The use of pasireotide could be considered before radiotherapy in a small number of selected patients. Radiotherapy is mainly used after surgery and can have a slow onset of efficacy (2–5 years). It often requires intermediate medical therapy and is associated with potentially threatening adverse events such as hypopituitarism, optic nerve damage, and increased risks of secondary malignancy.

3c. Does this medicine have the potential to make a significant and substantial impact on health related benefits?

In uncontrolled acromegaly patients, where medical treatment options have been exhausted and they still suffer the symptoms and long term implications of their disease, pasireotide offers an opportunity to give both biochemical and symptomatic control of their disease.

4. Added value of the medicine for the patient's family or carers

Acromegaly is a chronic and debilitating disorder, which can result in considerable burden of complications and co-existing illnesses, contributing to increased morbidity and mortality. Patients are often unable to continue with full-time employment and may rely on family support, both emotionally and financially. Family members have to take time out from their own personal commitments in order to provide care. Many patients with acromegaly suffer from psychological distress, and can suffer from depression, with subsequent adverse impact on their family. Patients report having significant stresses on their relationships and being unable to join in with family activities. Pasireotide provides patients with the opportunity to gain control of their disease, which can result in patients regaining independence and their lives returning to relative normality.

5. What is the most appropriate position for the medicine in the pathway of care for the condition? Does this differ from the company's proposed positioning?

Yes it does. The company state that the optimal positioning of pasireotide in the treatment of acromegaly is as second line medical therapy; i.e. in those patients for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue. This is in line with the licensed indication. The clinical expert referred to the information outlined in Section 2 and agreed to provide further clarity of the clinical pathway outside of the meeting.

6. Are there specific patient groups for whom the medicine is particularly beneficial? If so, please specify

As radiotherapy is associated with inevitable hypopituitarism, pasireotide might be considered before radiotherapy in a small number of selected cases; for example, young women who wish to retain fertility.

Additionally, pasireotide may be beneficial for those select few patients with significant tumour burden, which cannot be fully resected by surgery and is adjacent to the optic nerve, thereby risking visual impairment.

7. Are there any important considerations in relation to treatment delivery (e.g. how treatment should be monitored, how long it should be continued etc.)?

Pasireotide is given as a deep intramuscular injection, once every four weeks. Many

patients will be familiar with this routine, as a large proportion of patients will have previously received four-weekly treatment with a first generation somatostatin analogue.

8. Other considerations

Left untreated, patients with uncontrolled acromegaly suffer multiple co-morbidities, and as a result the financial impact on the NHS can be significantly more than if they were given effective treatment. For example, patients may need surgery to remove polyps or an annual colonoscopy due to the increased risk of bowel cancer, or may need to be on high doses of steroids and pain killers.

The company will be providing a Treatment Protocol Guidance document which outlines the use of pasireotide.

9. Is there a key factor, or combination of factors, that would justify this medicine being available in NHS Wales?

- The symptoms of acromegaly, and the co-morbidities associated with the disease, have an extensive impact on the patients' physical, mental and emotional health. Patients struggle to maintain daily routines, find it impossible to have a social life, and have significant stresses on their relationships.
- There is a definite unmet need for a small number of patients who are unable to control their condition through any other means; patients for whom surgery is not an option or has not been curative, patients who have been denied other treatments due to high costs, and patients who are inadequately controlled on treatment with a first generation somatostatin analogue. Pasireotide will provide an option to those who cause the greatest concern.
- Pasireotide is currently available in Scotland and a commissioning policy is currently being developed by NHS England. The use of pegvisomant has been declined through IPFR in Wales; due to the small number of patients with uncontrolled acromegaly it is difficult to demonstrate exceptionality. Clinicians expect it to be similarly difficult for pasireotide to be approved through IPFR. If pasireotide is not approved for use in Wales patients will be at a disadvantage over patients in the rest of the UK.
- Pasireotide can achieve biochemical control, halt or even reverse soft tissue symptoms, decrease tumour size, and help improve co-morbidities such as cardiomyopathy, hypertension or diabetes; all of which could translate into a gain in life expectancy. Improvements in physical health will have a considerable impact on the patient's psychological wellbeing.
- Pasireotide gives hope to a small group of patients, who are left with significantly impaired quality of life and expected premature death, and who would otherwise have no option but to continue living with this distressing condition.

It should be noted that one expert involved in compiling this response declared a personal specific interest in relation to pasireotide for the indication under consideration.