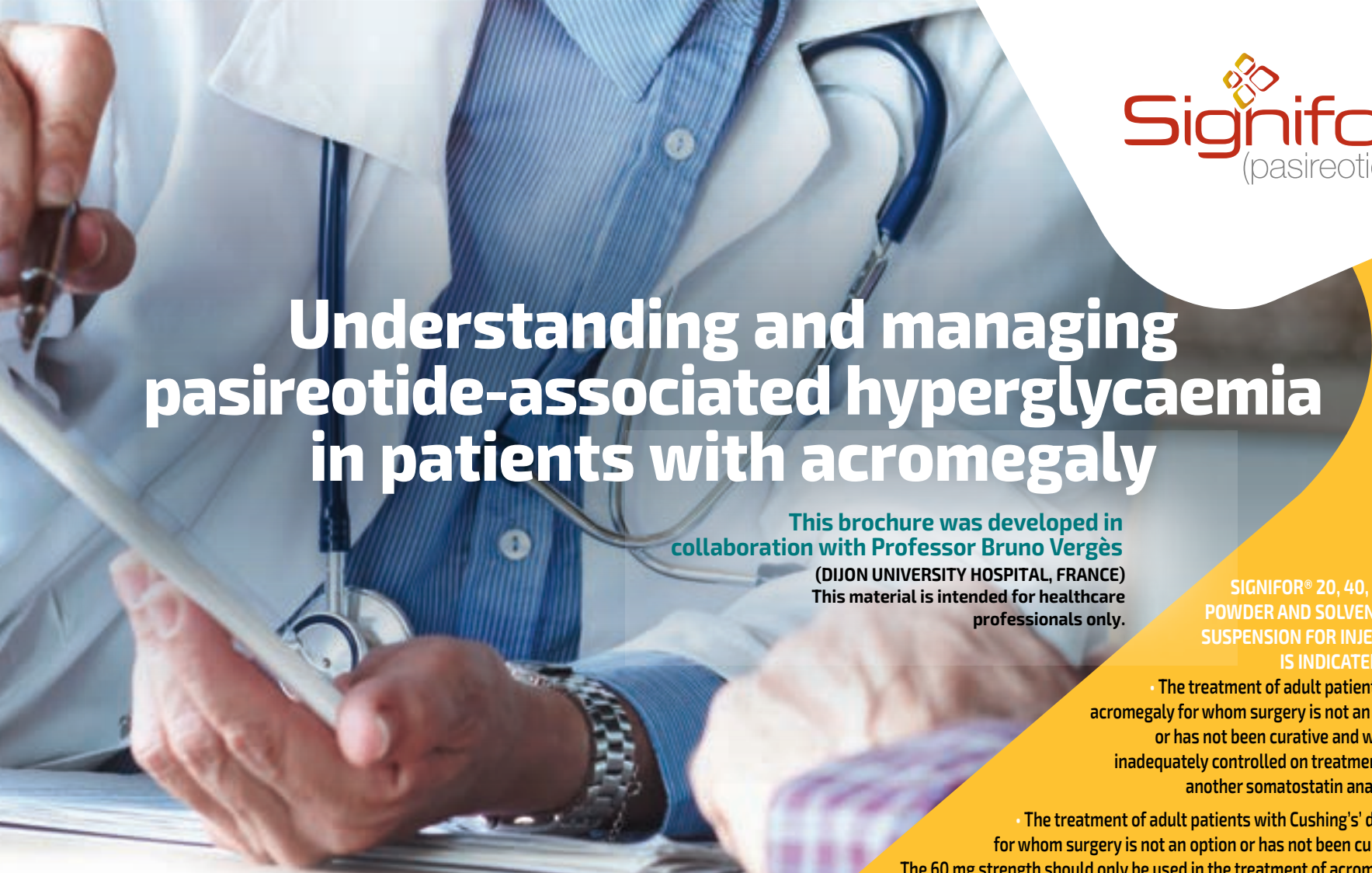


Signifor® (pasireotide)

Understanding and managing pasireotide-associated hyperglycaemia in patients with acromegaly

This brochure was developed in collaboration with Professor Bruno Vergès
(DIJON UNIVERSITY HOSPITAL, FRANCE)

This material is intended for healthcare professionals only.

SIGNIFOR® 20, 40, 60 mg POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION IS INDICATED 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.[1]
- The treatment of adult patients with Cushing's' disease for whom surgery is not an option or has not been curative.[1]

The 60 mg strength should only be used in the treatment of acromegaly.[1]
Signifor® 20, 40 and 60 mg is not reimbursed in Belgium for this indication.

SIGNIFOR® 0,6/0,9 MG SOLUTION FOR INJECTION IS INDICATED FOR:

- The treatment of adult patients with Cushing's' disease for whom surgery is not an option or has failed.[1]

Signifor® 0,6/0,9 mg is not available in Belgium.

BIOGRAPHY: Professor Bruno Vergès

Dijon University Hospital, Dijon, France

Bruno Vergès earned his Doctorate in Medicine in 1986 at Broussais-Hôtel Dieu Faculty of Medicine in Paris, France. As an intern in Paris hospitals, he specialised in endocrinology, diabetes and metabolic diseases. In November 1986, he was appointed Assistant Clinic Chief in Endocrinology and Diabetology at Dijon University Hospital. He did a postdoctoral fellowship in Brian Brewer's laboratories (National Institutes of Health, Bethesda, MD, USA) between 1990 and 1991, where he helped design and conduct kinetic studies of apolipoproteins with stable isotopes. He was appointed Professor of Endocrinology, Diabetology and Metabolic Diseases at the Faculty of Medicine of the University of Burgundy, Dijon, in November 1991.

Professor Vergès carries out his clinical practice at the Department of Endocrinology, Diabetology and Metabolic Diseases of Dijon University Hospital, where he is Head of Department. He also leads an INSERM research unit focusing on the pathophysiology of human dyslipidaemias (INSERM UMR 1231, Dijon). He has conducted numerous clinical studies and a large body of translational research, with international expertise in lipids and diabetes.

Professor Vergès was Secretary General of the French-speaking Diabetes Society (Société Francophone du Diabète [SFD]) in 2005 and 2006, Secretary General of the French Society of Endocrinology (Société Française d'Endocrinologie) in 2015 and 2016, and President of the Scientific Council of the SFD from March 2015 to March 2018. He is the author of more than 320 original publications in international journals and has given more than 600 presentations at national and international congresses. He was also involved in drafting several recommendations and expert consensus opinions (including on the management of hyperglycaemia under treatment with pasireotide).

The Department of Endocrinology, Diabetology and Metabolic Diseases of Dijon University Hospital is a reference centre for rare diseases of the pituitary gland (Centre de Référence des Maladies Rares de l'Hypophyse). Over the past 10 years, more than 110 patients with acromegaly have been treated at this department.

Summary

1. **Pasireotide, a second-generation somatostatin analogue**, has been shown to be **effective in patients with acromegaly resistant to first-generation** somatostatin receptor ligands (SRLs, such as octreotide and lanreotide), **with a beneficial effect on tumour control**.[2,3]

2. Pasireotide has a well-established and **manageable safety profile**, which is **similar to that of the first-generation** somatostatin analogues, **except for a higher frequency and degree of hyperglycaemia**.[2-4]

3. **Many patients do not develop pasireotide-associated hyperglycaemia**, however a number of **risk factors have been identified** as being associated with a higher likelihood of developing hyperglycaemia.[5,6]

4. Hyperglycaemia observed during pasireotide treatment is **manageable with oral antidiabetic therapies** in most patients, **without the need for treatment discontinuation**.[4,6]

5. For patients who do develop hyperglycaemia with pasireotide, **metformin is an effective initial treatment**, followed by incretin-based therapy if needed.[6]

Contents

How common are glucose metabolism disorders and how are they classified?

Abnormal glucose metabolism is common in patients with rare endocrine disorders, being reported in ~19–56% of patients with acromegaly[7] and up to ~70% of patients with endogenous Cushing's syndrome.[8] The prevalence of diabetes or impaired glucose tolerance (IGT) in patients with acromegaly ranges from 16–56% and 6–45%, respectively.[9]

In collaboration with the American Diabetes Association (ADA), the World Health Organisation has published a classification system to identify patients with abnormal glucose metabolism, based on fasting plasma glucose (FPG) levels and oral glucose tolerance test (OGTT), which reflect various degrees of hyperglycaemia that can lead to diabetes mellitus (DM) (Table 1).[10,11] More recently, with advancements in instrumen-tation and standardisation, an International Expert Committee also recommended the use of HbA_{1c} to diagnose diabetes, with a threshold of ≥6.5%.[12]

FPG, mg/dL (mmol/L)	Blood glucose 2 hours after glucose loading (75 g), mg/dL (mmol/L)		
	<140 (<7.8)	140–199 (7.8–11.0)	≥200 (≥11.1)
<100 (<5.6)	Normal glucose tolerance	Impaired glucose tolerance	Diabetes
100–125 (5.6–6.9)	Impaired fasting glucose	Impaired fasting glucose and impaired glucose tolerance	Diabetes
≥126 (≥7.0)	Diabetes	Diabetes	Diabetes

FPG, fasting plasma glucose

Table 1. World Health Organisation diagnostic criteria for diabetes mellitus and other categories of hyperglycaemia.[10,11]

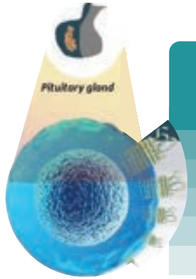
The ADA 2014 criteria define diabetes mellitus as HbA_{1c} ≥6.5% or FPG ≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL or a random plasma glucose ≥200 mg/dL[13]

Glucose metabolism disorders in patients with acromegaly or Cushing's syndrome can often be managed or improved with effective treatment. This educational brochure will focus on glucose metabolism abnormalities observed in patients with acromegaly treated with the novel somatostatin analogue, pasireotide.

What is pasireotide indicated for and how does it work?

Pasireotide is approved in the EU 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 first-generation somatostatin receptor ligands (SRLs).[1] Pasireotide has been shown to control both growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in medically-naïve patients with acromegaly as well as in patients uncontrolled on first generation SRLs.[2,3,6,14-16] Treatment with pasireotide has also shown to reduce tumour volume and improve clinical signs, symptoms and quality of life in patients with acromegaly.[2,3] Pasireotide has a well-established and manageable safety profile, which is similar to that of the first-generation somatostatin analogues, except for a higher frequency and degree of hyperglycaemia.[17]

Pasireotide is a multireceptor-targeted somatostatin analogue and somatostatin receptor type 2 (SSTR2),[1] thereby closely mimicking the activity of natural somatostatin. Because pasireotide targets a broader range of somatostatin receptors than first-generation SRLs, it might be expected to achieve biochemical responses in a wider population of patients with acromegaly (Figure 1).



Receptor	Molecule binding affinity*			
	Pasireotide	Somatostatin (SRIF-14)*	Lanreotide	Octreotide
SSTR5	0.16 ± 0.01	0.29 ± 0.04	17 ± 5	6.3 ± 1.0
SSTR2	1.0 ± 0.1	0.15 ± 0.02	0.54 ± 0.08	0.38 ± 0.08
SSTR1	9.3 ± 0.1	0.93 ± 0.12	180 ± 20	280 ± 80
SSTR3	1.5 ± 0.3	0.56 ± 0.17	14 ± 9	7.1 ± 1.4
SSTR4	>1000	1.5 ± 0.4	230 ± 40	>1000

Figure 1. Overview of somatostatin receptor binding profiles for octreotide, lanreotide and pasireotide[1]

*Results are the mean ± standard error of mean (SEM) of the half maximal inhibitory concentration (IC50) values expressed as nmol/L

Adapted from:
Bruns C , et al. European Journal of Endocrinology. 2002.

Pasireotide is a second-generation somatostatin analogue approved for the treatment of acromegaly that **targets four of the five SSTRs, with highest affinity for SSTR5**[1]

What is the pathophysiology of pasireotide-associated hyperglycaemia?

Based on the mechanism of action of pasireotide, hyperglycaemia is an expected side effect. Somatostatin receptors SSTR5 and SSTR2 also play important roles in blood glucose regulation; endogenous somatostatin inhibits insulin secretion via both SSTR5 and SSTR2 receptors, and glucagon secretion mainly by SSTR2.[19]

The mechanism of pasireotide-associated hyperglycaemia was evaluated in a randomised, open-label study of healthy male volunteers treated with pasireotide subcutaneous 600, 900 or 1200 µg twice a day for 7 days. Hyperglycaemia was shown to be related to decreases in insulin secretion and incretin hormone response:[20]

- During an oral glucose tolerance test (OGTT), the following was observed:
  - → Significant increase in blood glucose.
  - → Significant decrease in insulin and glucagon.
  - → Significant reduction in the secretion of incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).

During hyperinsulinaemic-euglycaemic clamp test:

No change in insulin sensitivity was observed.

Hyperglycaemia observed with pasireotide is secondary to a decrease in insulin secretion (particularly in the post-dose period) possibly caused by a direct effect of pasireotide on cells in the islets of Langerhans, **or a reduction in the secretion of GLP-1 and GIP** (Figure 2)[17]

The two mechanisms of hyperglycaemia are summarised below:

Figure 2. Overview of mechanisms of pasireotide-induced hyperglycaemia[17]

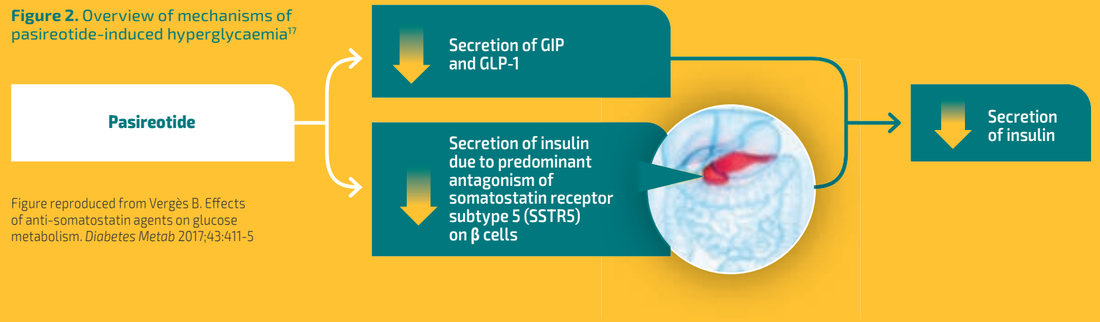


Figure reproduced from Vergès B. Effects of anti-somatostatin agents on glucose metabolism. *Diabetes Metab* 2017;43:411-5

1 Direct effect on the pancreas (Figure 3)

Endogenous somatostatin inhibits the secretion of insulin and glucagon via SSTR5 and SSTR2, respectively. Insulin is secreted by pancreatic β cells in the islets of Langerhans, which predominately express SSTR5, while glucagon is secreted by pancreatic α cells, which predominantly express SSTR2 (Figure 3a).[20,21]

As pasireotide binds with higher affinity to SSTR5 than SSTR2 (albeit in the pituitary adenoma, not the pancreas), a greater decrease in insulin secretion than glucagon secretion may occur, which can result in the development of hyperglycaemia (Figure 3b).[20,21]

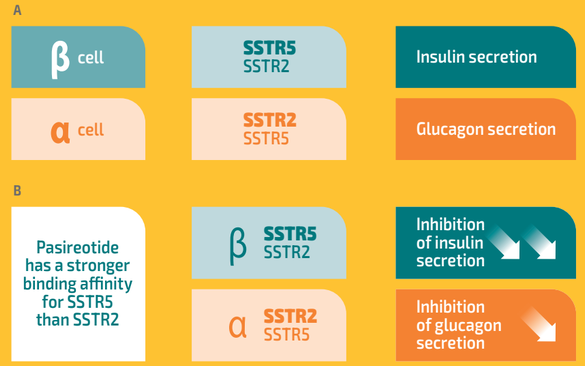


Figure 3. (**A**) Schematic representation of SSTR2 and SSTR5 expression on pancreatic α and β cells (**B**) Mechanism of action of pasireotide on pancreatic β and α cells via SSTR2 and SSTR5[20,21]

2 Decreased secretion of incretins (GIP, GLP-1)

Activation of SSTR5 by pasireotide leads to a reduction in GIP and GLP-1 secretion, which suppresses insulin secretion further and may also contribute to the development of hyperglycaemia.[20,21] A study carried out in healthy volunteers demonstrated that GIP and GLP-1 levels decreased from baseline after OGTT on days 1 and 8. However, the initial increase in GLP-1 and GIP levels following glucose ingestion on day 1 was not observed during OGTT on day 8 (Figure 4).[20]

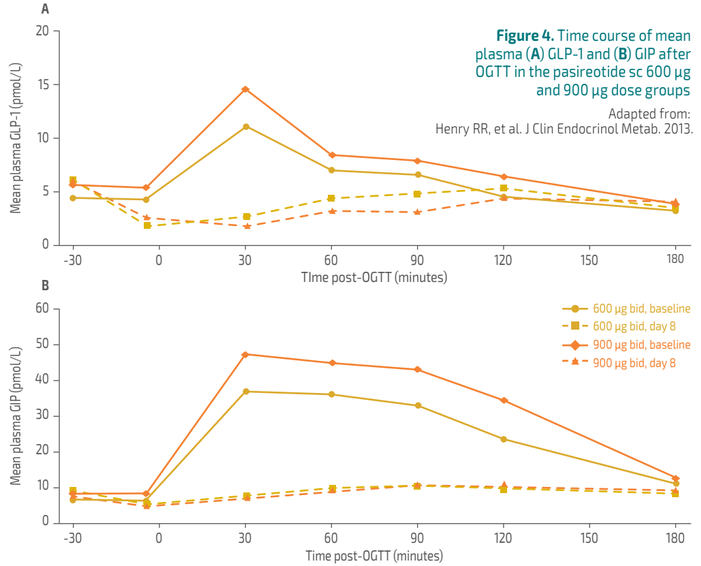


Figure 4. Time course of mean plasma (**A**) GLP-1 and (**B**) GIP after OGTT in the pasireotide sc 600 µg and 900 µg dose groups

Adapted from:
Henry RR, et al. J Clin Endocrinol Metab. 2013.

Pasireotide sc was administered at -30 minutes. bid, twice daily

As GIP and GLP-1 are hormones that stimulate insulin secretion in a glucosedependent manner, the marked reduction in their plasma levels with pasireotide appears to be an important factor involved in the observed decrease in insulin secretion.[20]

SSTR5 and SSTR2 also play **important roles in blood glucose regulation**. As such, **hyperglycaemia is an expected side effect** of treatment with pasireotide.[20]

How often did pasireotide-associated hyperglycaemia occur during the clinical trial programme and how was it managed?

Pasireotide was approved based on positive outcomes from a rigorous clinical trial programme. The Phase III study programme included 679 patients across three clinical trials.

The clinical trial programme highlighted that not all patients develop hyperglycaemia during pasireotide treatment, and it is manageable with proactive monitoring and early intervention without the need for treatment discontinuation (Figure 5).[4]

In clinical studies, rates of hyperglycaemia-related AEs were lower in patients with acromegaly than Cushing's disease, possibly resulting from differences in disease pathophysiology causing dysregulation of glucose metabolism, but may also be attributed to better understanding and management of pasireotide- associated hyperglycaemia during the clinical development program.[4]

This brochure focuses on key findings from the two pivotal Phase III studies in patients with acromegaly, C2402 (PAOLA)[3] and C2305[2] as well as the Phase IV B2219 study, which assessed incretin-based therapy versus insulin for managing pasireotide-associated hyperglycaemia that was uncontrolled with metformin or other oral antidiabetic drugs (OADs) in patients with acromegaly and Cushing's disease.[6]

Figure 5. Frequency of pasireotide-associated hyperglycaemia-related adverse events in patients with acromegaly[4]

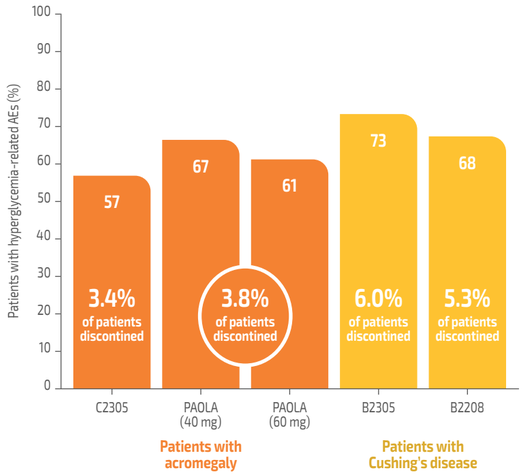


Figure adapted from Silverstein JM. Hyperglycemia induced by pasireotide in patients with Cushing's disease or acromegaly. *Pituitary* 2016;19:536-43

PAOLA: pasireotide LAR 40 mg and 60 mg versus active control [octreotide LAR or lanreotide] in patients with inadequately controlled acromegaly; C2305: pasireotide LAR 40 mg versus octreotide in medically-naïve patients with acromegaly

Occurrence of hyperglycaemia in the PAOLA study – key findings

- PAOLA was a 24-week randomised, parallel group study of pasireotide LAR 40 mg (n=65) and 60 mg (n=65) versus active control (octreotide LAR or lanreotide; n=68) in patients with inadequately controlled acromegaly.[3]
  - At 24 weeks, ten (15%) patients in the pasireotide 40 mg group and 13 (20%) patients in the pasireotide 60 mg group achieved biochemical control (mean GH concentration <2.5 µg/L and normalised IGF-1), compared with no patients in the active control group.
- A higher proportion of patients treated with pasireotide experienced AEs of hyperglycaemia and diabetes mellitus suspected to be related to study treatment than those in the active control group (Table 2).[3]

AE, n (%)	Pasireotide 40 mg (n=63)	Pasireotide 60 mg (n=62)	Active control (n=66)
Hyperglycaemia	21 (33.3)	18 (29.0)	4 (6.1)
Diabetes mellitus	12 (19.0)	16 (25.8)	3 (4.5)

Table 2. Proportion of patients with AEs of hyperglycaemia or diabetes mellitus suspected to be related to study treatment[3]

Figure Adapted from: Gadelha MR, et al. Lancet Diabetes Endocrinol. 2014.

- There were only a few cases of grade 3 (indication for hospitalisation to initiate insulin therapy) and grade 4 (emergency hospitalisation as a result of a life-threatening prognosis) hyperglycaemia and diabetes mellitus AEs with pasireotide treatment[3].

AE, n (%)	Pasireotide 40 mg (n=63)	Pasireotide 60 mg (n=62)	Active control (n=66)
Hyperglycaemia	7 (11.1)	5 (8.1)	0
Diabetes mellitus	0	2 (3.2)	0

Table 3. Incidence of grade 3/4 AEs of hyperglycaemia and diabetes mellitus suspected to be related to study treatment[3]

Adapted from: Gadelha MR, et al. Lancet Diabetes Endocrinol. 2014.

Most patients did not develop pasireotide-associated hyperglycaemia. In patients that did, the majority of hyperglycaemia-related AEs were grade 1/2 and **few patients discontinued treatment** as a result.[3]

- Both mean FPG and HbA1c levels increased from baseline with pasireotide 40 mg and 60 mg during the study (Table 4).[3]

	FPG, mg/dL	HbA_{1c}, %
Pasireotide 40 mg	25	0.7
Pasireotide 60 mg	35	0.9

Table 4. Mean increase in FPG and HbA_{1c} levels from baseline to week 24 with pasireotide[3]

Adapted from: Gadelha MR, et al. Lancet Diabetes Endocrinol. 2014.

Mean FPG and HbA_{1c} concentrations initially increased from baseline during the first 3 months of treatment, then stabilised up to week 24 (Figure 6)[3]

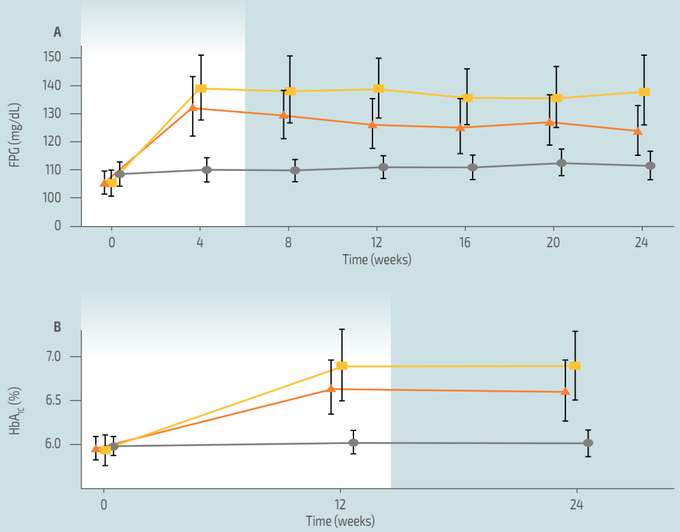


Figure 6. Mean (**A**) FPG and (**B**) HbA_{1c} levels over time[3]

Adapted from: Gadelha MR, et al. Lancet Diabetes Endocrinol. 2014.

FPG and HbA_{1c} levels increase soon after pasireotide initiation and then stabilised. As such, hyperglycaemia-related AEs are most likely to occur during the first few months after initiating treatment.[3]

Reversibility of pasireotide-associated hyperglycaemia

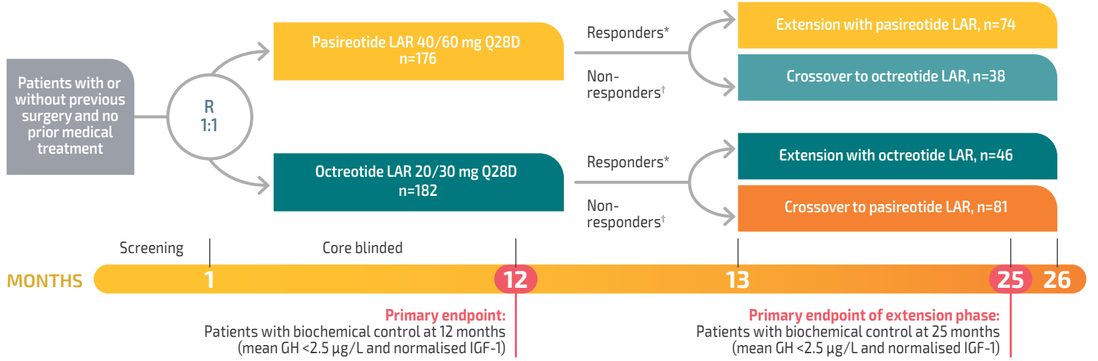
Hyperglycaemia induced by pasireotide LAR is reversible upon discontinuation of treatment, as exemplified in the C2305 study (Figure 7).[2,14,15]

Figure 7. Overview of the C2305 study design.

*Responder: GH <2.5 µg/L and normal IGF-1 at month 12;

†Non-responder: neither a responder nor a partial responder (partial responder: GH <5 µg/L and IGF-1 ≤1.3 x ULN but not biochemical control)

GH, growth hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting release; Q28D, once every 28 days



Adapted from: Colao A, et al. J Clin Endocrinol Metab. 2014.

Within 3 months of switching from pasireotide LAR to octreotide LAR, mean FPG and HbA_{1c} levels decreased towards core baseline levels; levels at month 3 were similar to those reported at core baseline (mean FPG: 103.8 vs 97.8 mg/dL; mean HbA_{1c}: 6.1% vs 5.9%; Figure 8).[5,14]

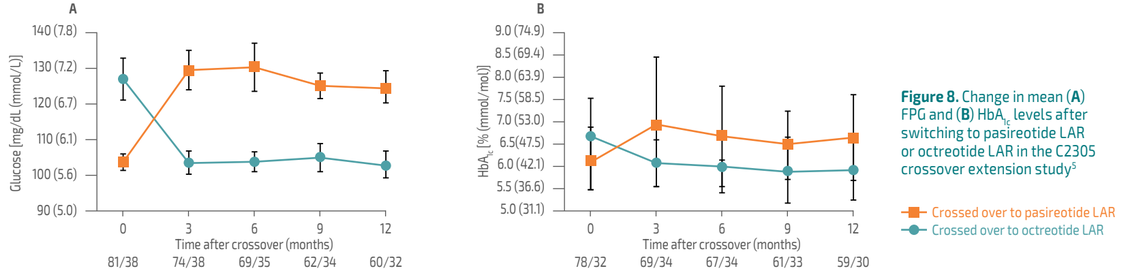


Figure 8. Change in mean (**A**) FPG and (**B**) HbA_{1c} levels after switching to pasireotide LAR or octreotide LAR in the C2305 crossover extension study[5]

Numbers below the horizontal axes refer to the number of patients who crossed over to long-acting pasireotide/crossed over to long-acting octreotide.

Adapted from: Gadelha MR, et al. Lancet Diabetes Endocrinol. 2014.

Pasireotide-associated **hyperglycaemia is reversible upon discontinuation** of pasireotide.[5]

Management of pasireotide-associated hyperglycaemia in clinical trials

For most patients who develop hyperglycaemia, metformin alone or in combination with other oral antidiabetics are effective initial treatments.[3,6]

→ In PAOLA, antidiabetic treatment was initiated during the study in 24 (38%) patients in the pasireotide LAR 40 mg group, 24 (39%) patients in the pasireotide LAR 60 mg group, and 4 (6%) patients in the active control group (including patients who had or had not received antidiabetic treatment before inclusion in the study, most commonly metformin; Figure 9).[3]

- The percentage of patients not previously treated with antidiabetic medication who started antidiabetic treatment during the study was 17.5% and 16.1% in the pasireotide LAR 40 mg and 60 mg groups, respectively, compared with 1.5% in the active control group.[1]

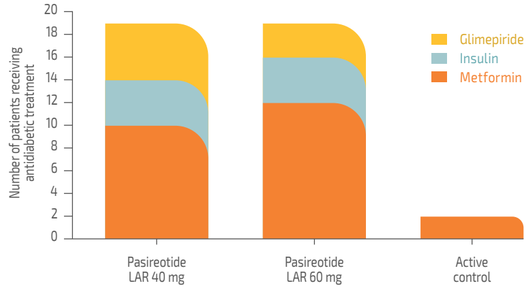


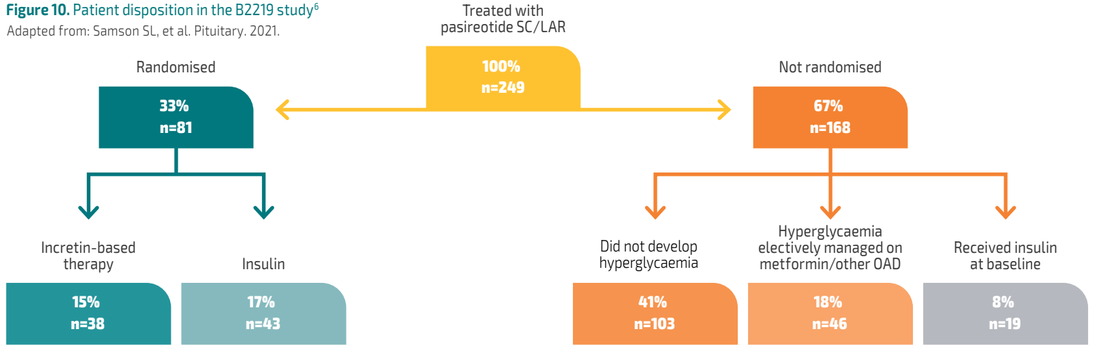
Figure 9. Overview of antidiabetic treatment initiated during the PAOLA study
Adapted from: Gadelha MR, et al. J Clin Endocrinol Metab. 2014

The majority of patients can be **managed using oral antidiabetic medication** (OAD).[6]

→ The Phase IV trial (B2219) was prospectively designed to assess the efficacy of incretin-based therapy versus insulin in the management of pasireotide-associated hyperglycaemia that is uncontrolled with metformin or other OADs in patients with acromegaly or Cushing's disease.[6]

- Patients who developed pasireotide-associated hyperglycaemia and had FPG >126 mg/dL despite management with metformin or other OADs were randomised to receive **incretin-based therapy** (n=38/249) or **insulin** (n=43/249; Figure 10).

Figure 10. Patient disposition in the B2219 study[6]
Adapted from: Samson SL, et al. Pituitary. 2021.



- **41.4% of patients** with either acromegaly (n=190) or Cushing's disease (n=59) who were treated with pasireotide **did not develop hyperglycaemia** requiring antidiabetic medication; **49.7% of patients with acromegaly did not develop hyperglycaemia** requiring antidiabetic medication.[6]
- 46 patients who developed pasireotide-associated hyperglycamia were **effectively managed with metformin or other OADs** (non-incretin-based therapies, eg acarbose and sulfonylureas).[6]
- **Incretion-based theraphy was more effective** in the managment of pasireotide-associated hyperglycaemia **than insulin**; adjusted mean change in HbA1c between treatment arms was -0.28% (95% confidence interval -0.63, 0.08) in favour of incretin-based therapy.[6]

Though **49.7% of patients with acromegaly did not develop pasireotide-associated hyperglycaemia**, for those patients who did, **metformin was an effective initial treatment**, followed by incretin-based therapy if needed.[6]

→ In a Phase I, open-label study of healthy volunteers, dipeptidyl peptidase 4 (DPP4) inhibitors and GLP-1 agonists were more effective in minimising pasireotide-associated hyperglycaemia than other antidiabetic treatments (eg metformin, glinides).[23]

What are the risk factors associated with the development of hyperglycaemia with pasireotide?

A number of patient characteristics have been identified, which indicate the likelihood of developing hyperglycaemia:

1 The glycaemic status of patients at baseline

→ Patients with normal glucose tolerance at baseline were less likely to develop hyperglycaemia-related AEs than patients with pre-diabetic or diabetic status (Table 5).[3]

Table 5. Proportion of patients with hyperglycaemia-related AEs in the PAOLA study, regardless of study drug relationship.[3]

	Pasireotide 40 mg n=63	Pasireotide 60 mg n=62	Active control n=66
Hyperglycaemia-related AEs, n (%)	42 (66.7)	38 (61.3)	20 (30.3)
By baseline diabetic status:			
Diabetic	32/45 (71.1)	26/37 (70.3)	10/46 (21.7)
Pre-diabetic	7/10 (70.0)	6/12 (50.0)	10/18 (55.5)
Normal glucose tolerance	3/8 (37.5)	6/13 (46.2)	0/2

Diabetic: FPG ≥126 mg/dL or glycated haemoglobin (HbA_{1c}) ≥6.5%; pre-diabetic: FPG 100–<126 mg/dL or HbA_{1c} 5.7–<6.5%; normal glucose tolerance: FPG <100 mg/dL and/or HbA_{1c} <5.7%

→ The development of hyperglycaemia with pasireotide was significantly more frequent among patients with baseline FPG >100 mg/dL than in patients with baseline FPG ≤100 mg/dL (Table 6).[24]

Table 6. Proportion of patients developing pasireotide-associated hyperglycaemia based on FPG at baseline in the PAOLA study.[24]

	FPG ≤100 mg/dL	FPG >100 mg/dL
Pasireotide LAR 40 mg	30%	52%
Pasireotide LAR 60 mg	48%	71%

Hyperglycaemia occurs less frequently with pasireotide **when blood glucose levels are normal before the start of treatment** than for patients with pre-existing hyperglycaemia.[4,24]

2 Other factors identified from PAOLA and C2305:[5,24]

- **Age (>40 years in PAOLA and >30 years in C2305)**
- **History of hypertension (C2305)**
- **Body mass index ≥30 kg/m² (PAOLA)**
- **History of dyslipidaemia (C2305)**

In the PAOLA study, the **frequency of hyperglycaemia** with pasireotide LAR treatment was **similar in patients who were responders** (GH <2.5 µg/L and normal IGF-1) **and non-responders** (GH ≥2.5 µg/L and/or IGF-1 above the upper limit of normal) and was **dependent on the baseline FPG level**.[24]

What are the recommendations for screening and management of hyperglycaemia induced by pasireotide?

Recommendations for the screening and management of pasireotide-associated hyperglycaemia in clinical practice are supported by medical expert consensus:[1,22,25]

Blood glucose monitoring when initiating treatment with pasireotide (Figure 11)

- Levels of FPG and HbA1c should be assessed in all patients prior to initiating pasireotide treatment[1,25]
- Regular self-monitoring of blood glucose (SMBG) and/or FPG assessments is advised during treatment, as clinically appropriate[1]
- If FPG is <126 mg/dL (<7 mmol/L) and HbA1c is <6.5%, self-monitoring of fasting and postprandial capillary blood glucose is advised at least 1-2 times per week during the first week of treatment, then once a week during the first 3 months[1,22,25]
- If the patient is diabetic (FPG ≥126 mg/dL [≥7 mmol/L] and HbA_{1c} ≥6.5%), daily self-monitoring of fasting and postprandial capillary blood glucose is advised 3–7 times a week[22]
- Self-monitoring of blood glucose and/or FPG assessments is also advised over the first four to six weeks after any dose increase[1]

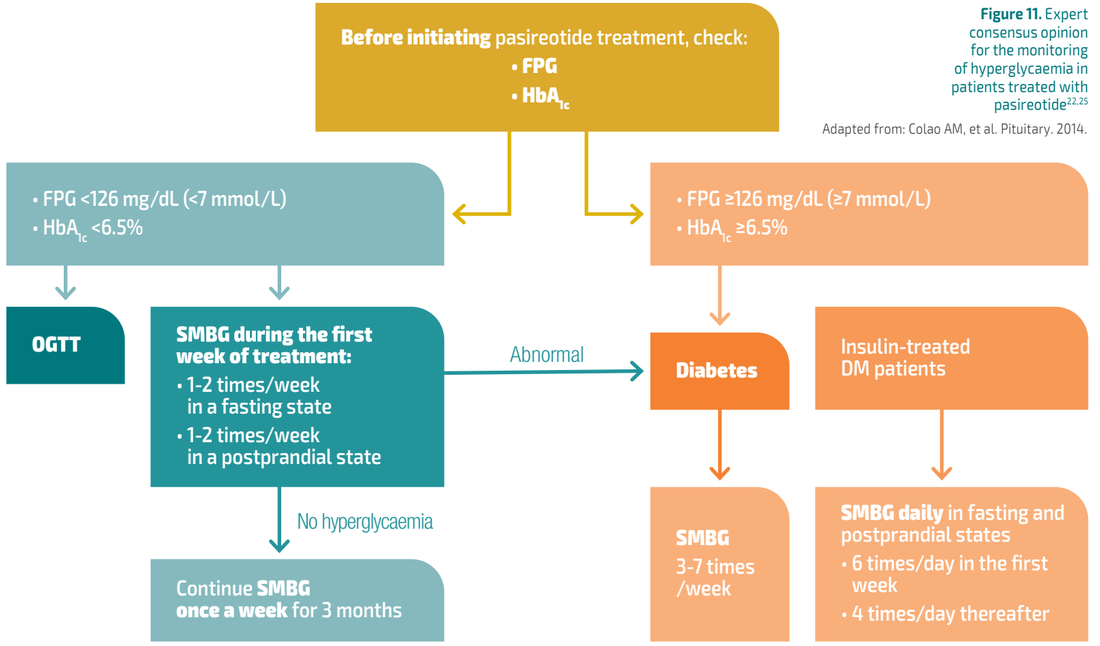


Figure 11. Expert consensus opinion for the monitoring of hyperglycaemia in patients treated with pasireotide[22,25]

Adapted from: Colao AM, et al. Pituitary. 2014.

Blood glucose should be monitored regularly during pasireotide treatment, particularly **during the first 3 months**, with special attention given to patients with pre-existing impaired glucose tolerance or diabetes.[22]

Current recommendations for the management of patients who develop hyperglycaemia with pasireotide LAR treatment (Figure 12)[22,25]

- If hyperglycaemia develops in a patient being treated with pasireotide, the initiation or adjustment of antidiabetic treatment is recommended following the established treatment guidelines for the management of hyperglycaemia[1]
- Management of hyperglycaemia should include dietary modifications, exercise and education[22]
- If HbA_{1c} >7%, initiate antidiabetic treatment:[22,25]
  - DPP-4 inhibitors
  - Metformin if there is evidence of insulin resistance (abdominal obesity)[22]
- If HbA_{1c} >7% on monotherapy, switch to combination therapy:[22,25]
  - Metformin + DPP-4 inhibitors initially
  - If insufficient, replace DPP-4 inhibitor with GLP-1 agonist + metformin.
  - If hyperglycaemia remains uncontrolled, initiate insulin treatment while maintaining metformin.

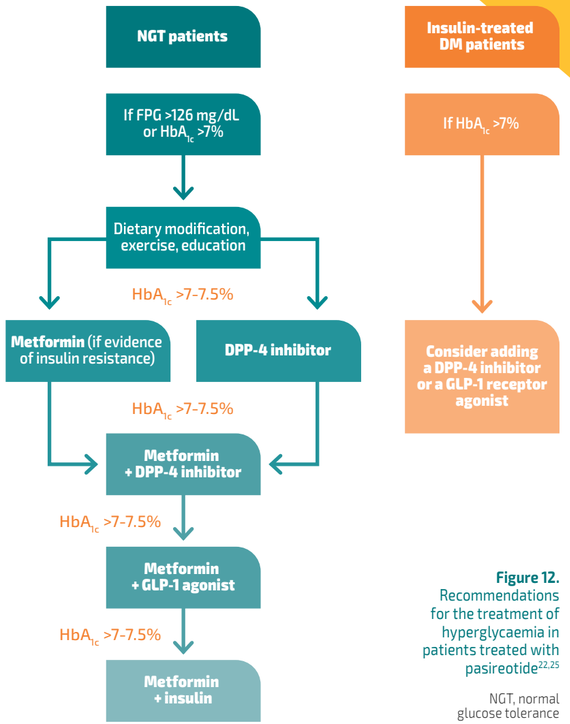


Figure 12. Recommendations for the treatment of hyperglycaemia in patients treated with pasireotide[22,25]

NGT, normal glucose tolerance

Adapted from: Colao AM, et al. Pituitary. 2014.

CONCLUSIONS

- **Pasireotide**, a second-generation somatostatin analogue, has been shown to be **effective in reducing IGF-1 and GH levels** in patients with acromegaly resistant to first-generation somatostatin analogues, **with a beneficial effect on tumour control**.
- Because of its mode of action, pasireotide can cause alterations in glucose metabolism in some patients, and therefore **blood glucose should be monitored** during treatment, particularly **during the first 3 months**.
- Pasireotide-associated **hyperglycaemia is reversible and can be managed in most patients with oral antidiabetic therapy**.
  - Most patients do not need to discontinue treatment with pasireotide.
  - Metformin or incretin-based treatments (DPP-4 inhibitors or GLP-1 agonists) are effective therapies.
  - Incretin-based treatments are particularly recommended in this situation, as the glucose metabolism abnormalities induced by pasireotide are, in part, linked to a marked reduction in the secretion of GIP and GLP-1.

Pasireotide has been shown to provide **biochemical control alongside improvements in tumour volume, clinical signs, symptoms and quality of life** in patients with acromegaly. **Many patients do not develop hyperglycaemia** during pasireotide treatment, **which is manageable** with proactive monitoring and early intervention **without the need for treatment discontinuation**.

REFERENCES

1. Signifor® summary of product characteristics, latest version
2. Colao A, Bronstein MD, Freda P et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. *J Clin Endocrinol Metab* 2014;99:791-9.
3. Gadelha MR, Bronstein MD, Brue T et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, Phase 3 trial. *Lancet Diabetes Endocrinol* 2014;2:875-84.
4. Silverstein JM. Hyperglycemia induced by pasireotide in patients with Cushing's disease or acromegaly. *Pituitary* 2016;19:536-43.
5. Gadelha MR, Gu F, Bronstein MD et al. Risk factors and management of pasireotide-associated hyperglycemia in acromegaly. *Endocr Connect* 2020;9:1178-90.
6. Samson SL, Gu F, Feldt-Rasmussen U et al. Managing pasireotide-associated hyperglycemia: a randomized, open-label, Phase IV study. *Pituitary* 2021;24:887-903.
7. Urbani C, Sardella C, Calevro A et al. Effects of medical therapies for acromegaly on glucose metabolism. *Eur J Endocrinol* 2013;169:99-108.
8. Scaroni C, Zilio M, Foti M et al. Glucose metabolism abnormalities in Cushing syndrome: from molecular basis to clinical management. *Endocr Rev* 2017;38:189-219.
9. Ferraù F, Albani A, Ciresi A et al. Diabetes Secondary to Acromegaly: Physiopathology, Clinical Features and Effects of Treatment. *Frontiers in Endocrinology* 2018;9.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014;37(Suppl 1):S81-90.
11. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia 2006. Available at: https://apps.who.int/iris/bitstream/handle/10665/43588/9241594934_eng.pdf?sequence=1&isAllowed=y).
12. International Expert C. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327-34.
13. American Diabetes A. Standards of medical care in diabetes-2014. *Diabetes Care* 2014; 37 Suppl 1: S14-80.
14. Bronstein MD, Fleseriu M, Neggers S et al. Switching patients with acromegaly from octreotide to pasireotide improves biochemical control: crossover extension to a randomized, double-blind, Phase III study. *BMC Endocr Disord* 2016;16:16.
15. Sheppard M, Bronstein MD, Freda P et al. Pasireotide LAR maintains inhibition of GH and IGF-1 in patients with acromegaly for up to 25 months: results from the blinded extension phase of a randomized, double-blind, multicenter, Phase III study. *Pituitary* 2015;18:385-94.
16. Gadelha M, Bex M, Colao A et al. Evaluation of the efficacy and safety of switching to pasireotide in patients with acromegaly inadequately controlled with first-generation somatostatin analogs. *Front Endocrinol (Lausanne)* 2019;10:931.
17. Vergès B. Effects of anti-somatostatin agents on glucose metabolism. *Diabetes Metab* 2017;43:411-5.
18. Bruns C, Lewis I, Briner U et al. SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. *Eur J Endocrinol* 2002;146:707-16.
19. Kumar U, Sasi R, Suresh S et al. Subtype-selective expression of the five somatostatin receptors (hSSTR1-5) in human pancreatic islet cells: a quantitative double-label immunohistochemical analysis. *Diabetes* 1999;48:77-85.
20. Henry RR, Ciaraldi TP, Armstrong D et al. Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers. *J Clin Endocrinol Metab* 2013;98:3446-53.
21. Poullot AG, Chevalier N. New options in the treatment of Cushing's disease: a focus on pasireotide *Res Rep Endocr Disord* 2013;3:31-8.
22. Colao A, De Block C, Gaztambide MS et al. Managing hyperglycemia in patients with Cushing's disease treated with pasireotide: medical expert recommendations. *Pituitary* 2014;17:180-6.
23. Breitschaft A, Hu K, Hermosillo Reséndiz K et al. Management of hyperglycemia associated with pasireotide (SOM230): healthy volunteer study. *Diabetes Res Clin Pract* 2014;103:458-65.
24. Schmid HA, Brue T, Colao A et al. Effect of pasireotide on glucose- and growth hormone-related biomarkers in patients with inadequately controlled acromegaly. *Endocrine* 2016;53:210-9.
25. Reznik Y, Bertherat J, Borson-Chazot F et al. Management of hyperglycaemia in Cushing's disease: experts' proposals on the use of pasireotide. *Diabetes Metab* 2013;39:34-41.

LIST OF ABBREVIATIONS

ADA, American Diabetes Association

AE, adverse event

DM, diabetes mellitus

DPP-4, dipeptidyl peptidase 4

FPG, fasting plasma glucose

GH, growth hormone

GIP, glucose-dependent insulinotropic polypeptide

GLP-1, glucagon-like peptide 1

HbA1c, glycated haemoglobin

IC50, half-maximal inhibitory concentration

IGF-1, insulin-like growth factor 1

IGT, impaired glucose tolerance

LAR, long-acting release

NGT, normal glucose tolerance

OAD, oral antidiabetic drug

OGTT, oral glucose tolerance test

Q28D, once every 28 days

R, randomised

SC, subcutaneous

SEM, standard error of the mean

SFD, Secretary General of the French-speaking Diabetes Society

SMBG, self-monitoring of blood glucose

SRL, somatostatin receptor ligand

SSTR, somatostatin receptor

ULN, upper limit of normal

NAME OF THE MEDICINAL PRODUCT Signifor 20 mg powder and solvent for suspension for injection. Signifor 40 mg powder and solvent for suspension for injection. Signifor 60 mg powder and solvent for suspension for injection. **QUALITATIVE AND QUANTITATIVE COMPOSITION** One vial contains respectively 20 mg, 40 mg or 60 mg pasireotide (as pasireotide pamoate). **PHARMACEUTICAL FORM** Powder and solvent for suspension for injection (powder for injection). Powder: slightly yellowish to yellowish powder. Solvent: clear, colourless to slightly yellow or slightly brown solution. **THERAPEUTIC INDICATIONS** 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. Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. The 60 mg strength is only to be used in the treatment of acromegaly. **POSOLOGY AND METHOD OF ADMINISTRATION** Posology *Acromegaly* The recommended initial dose for the treatment of acromegaly is 40 mg of pasireotide every 4 weeks. The dose may be increased to a maximum of 60 mg for patients whose growth hormone (GH) and/or insulin-like growth factor-1 (IGF-1) levels are not fully controlled after 3 months of treatment with Signifor at 40 mg. Management of suspected adverse reactions or over-response to treatment (IGF-1 < lower limit of normal) may require temporary dose reduction of Signifor. The dose may be decreased either temporarily or permanently. *Cushing's disease* The recommended initial dose for the treatment of Cushing's disease is 10 mg of pasireotide by deep intramuscular injection every 4 weeks. The patient should be evaluated for clinical benefit after the first month of treatment and periodically thereafter. The dose may be titrated every 2 to 4 months based on response and tolerability. The maximum dose of Signifor in Cushing's disease is 40 mg every 4 weeks. If no clinical benefit is observed, the patient should be considered for discontinuation. Management of suspected adverse reactions or over-response to treatment (cortisol levels < lower limit of normal) may require dose reduction, interruption or discontinuation of Signifor. *Switch from subcutaneous to intramuscular formulation in Cushing's disease* There are no clinical data available on switching from the subcutaneous to the intramuscular pasireotide formulation. If such a switch should be required, the recommended initial dose for the treatment of Cushing's disease is 10 mg of pasireotide by deep intramuscular injection every 4 weeks. The patient should be monitored for response and tolerability and further dose adjustments may be needed. *Missed dose* If a dose of Signifor is missed the missed injection should be administered as soon as possible. The next dose should then be planned for 4 weeks after the injection is administered in order to resume the normal schedule of one dose every 4 weeks. *Special populations Elderly patients (≥65 years)* Data on the use of Signifor in patients older than 65 years are limited, but there is no evidence to suggest that dose adjustment is required in these patients. *Renal impairment* No dose adjustment is required in patients with impaired renal function. *Hepatic impairment* Dose adjustment is not required in patients with mildly impaired hepatic function (Child Pugh A). Acromegaly: the recommended initial dose for acromegaly patients with moderate hepatic impairment (Child Pugh B) is 20 mg every 4 weeks, and the maximum recommended dose for these patients is 40 mg every 4 weeks. Cushings disease: the recommended initial dose for Cushing's disease patients with moderate hepatic impairment (Child Pugh B) is 10 mg every 4 weeks, and the maximum recommended dose for these patients is 20 mg every 4 weeks. Signifor should not be used in patients with severe hepatic impairment (Child Pugh C). *Paediatric population* The safety and efficacy of Signifor in children and adolescents aged 0 to 18 years have not been established. No data are available. Method of administration Signifor is to be administered by deep intramuscular injection by a trained healthcare professional. Signifor suspension must only be prepared immediately before administration. The site of repeat intramuscular injections should be alternated between the left and right gluteal muscle. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. Severe hepatic impairment (Child Pugh C). **UNDESIRABLE EFFECTS** Summary of the safety profile The safety profile of pasireotide intramuscular use is consistent with the somatostatin analogue class, except for the higher degree and frequency of hyperglycaemia seen with pasireotide intramuscular use. The safety profile of pasireotide intramuscular use was largely similar between the acromegaly and Cushing's disease indications. *Acromegaly* In acromegaly, the safety assessment was made based on 491 patients who received pasireotide (419 patients received pasireotide intramuscular use and 72 received pasireotide subcutaneous use) in phase I, II and III studies. The most common adverse reactions (incidence ≥1/10) from the pooled safety data from the phase III studies C2305 and C2402 were (in decreasing order): diarrhoea (most common in study C2305), cholelithiasis, hyperglycaemia (most common in study C2402) and diabetes mellitus. *Common Toxicity Criteria* (CTC) Grade 3 and 4 adverse reactions were mostly related to hyperglycaemia. *Cushing's disease* In Cushing's disease, the safety assessment of the intramuscular formulation was made based on 150 patients who received pasireotide in the phase III study G2304 (median duration of exposure: 57 weeks). Patients were randomised in a 1:1 ratio to receive starting doses of either 10 mg or 30 mg pasireotide, with a possibility to up-titrate to a maximum dose of 40 mg every 28 days. The most common adverse reactions (incidence ≥1/10) in the phase III study G2304 were hyperglycaemia, diarrhoea, cholelithiasis and diabetes mellitus. The frequency and severity of adverse reactions tended to be higher with the higher starting dose of 30 mg, but this was not consistent for all adverse reactions. List of adverse reactions The adverse reactions in the List include events reported in the pivotal studies with the intramuscular formulation in patients with acromegaly and with Cushing's disease. Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies were defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); not known (cannot be estimated from the available data). **Blood and lymphatic system disorders** Common: Anaemia. **Endocrine disorders** Common: Adrenal insufficiency*. **Metabolism and nutrition disorders** Very common: Hyperglycaemia, diabetes mellitus; Common: Type 2 diabetes mellitus, glucose tolerance impaired, decreased appetite; Not known: Diabetic ketoacidosis. **Nervous system disorders** Common: Headache, dizziness. **Cardiac disorders** Common: Sinus bradycardia*, QT prolongation. **Gastrointestinal disorders** Very common: Diarrhoea, nausea, abdominal pain*; Common: Abdominal distension, vomiting; Not known: Steatorrhea, Faeces discoloured. **Hepatobiliary disorders** Very common: Cholelithiasis; Common: Cholecystitis*, cholestasis. **Skin and subcutaneous tissue disorders** Common: Alopecia, pruritus. **General disorders and administration site conditions** Very common: fatigue*; Common: Injection site reaction*. **Investigations** Common: Glycosylated haemoglobin increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood glucose increased, blood creatine phosphokinase increased, lipase increased; Uncommon: Amylase increased, prothrombin time prolonged. * Grouped terms: Adrenal insufficiency includes adrenal insufficiency and blood cortisol decreased. Sinus bradycardia includes bradycardia and sinus bradycardia. Abdominal pain includes abdominal pain and abdominal pain upper. Injection site reaction includes injection site pain, injection site nodule, injection site discomfort, injection site bruising, injection site pruritus, injection site reaction, injection site hypersensitivity and injection site swelling. Cholecystitis includes cholecystitis acute and cholecystitis chronic. Fatigue includes fatigue and asthenia. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: Belgium: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten, www.fagg.be, Afdeling Vigilantie, Website: www.eenbijwerkingmelden.be, e-mail: adr@fagg-afmps.be. Luxembourg: Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé Site internet : www.guichet.lu/pharmacovigilance **MARKETING AUTHORISATION HOLDER** Recordati Rare Diseases, Immeuble Le Wilson, 70 avenue du Général de Gaulle, 92800 Puteaux, France **MARKETING AUTHORISATION NUMBER(S)** Signifor 20 mg powder and solvent for suspension for injection EU/1/12/753/013 Signifor 40 mg powder and solvent for suspension for injection EU/1/12/753/014 Signifor 60 mg powder and solvent for suspension for injection EU/1/12/753/016 **DELIVERY METHOD** Medicinal product subject to medical prescription. **DATE OF REVISION OF THE TEXT** 06/2024

Signifor® (pasireotide)

Recordati BV
Recordati Rare Diseases Benelux
Burgemeester Etienne Demunterlaan 5, 1090 Jette - Belgium
Phone: +32 2 461 01 36
Email: RRDBeneluxinfo@recordati.com

To report an adverse event, please inform your local Recordati Rare Diseases contact or mail to **rrdpharmacovigilance@recordati.com**
This brochure is intended for healthcare professionals only

RECORDATI RARE DISEASES

www.recordatirarediseases.com
Follow us on LinkedIn

BE-SIG-0006
Date of approval material: 10/2024