



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

TGA Health Safety
Regulation

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Regulation

March 2014

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACTH	Adrenocorticotrophic hormone
AE	Adverse event
AMS	Accelerator mass spectrometry
AST	Aspartate aminotransferase
AUC	Area under curve
BD	Twice daily
BMI	Body mass index
BW	Body weight
C _{max}	Maximum concentration
CL/F	Apparent plasma clearance
CMI	Consumer Medicine Information
CTCAE	Common terminology criteria for adverse events
EMA	European Medicines Authority
EU	European Union
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GDR	Glucose disposal rate
GEP	Gastro entero pancreatic
GGT	Gamma-glutamyltransferase
GH	Growth hormone
GHRH	Growth hormone releasing hormone
GI	Gastrointestinal
HPLC	High-performance liquid chromatography
HV	Healthy volunteers
IGF	Insulin like growth factor

Abbreviation	Meaning
IGFBP	Insulin like growth factor binding protein
IVRS	Interactive voice response system
PD	Pharmacodynamic
PI	Product Information
PK	Pharmacokinetic
SAE	Serious adverse event
sc	Subcutaneous
SCS	Summary of Clinical Safety
SD	Standard deviation
SE	Standard error
SSTR	Somatostatin receptors
TGA	Therapeutic Goods Administration
$t_{1/2}$	Half life
T_{max}	Time to maximum concentration
UFC	Urinary free cortisol
ULN	Upper limit of normal

Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	28 October 2013
<i>Active ingredient:</i>	Pasireotide (as diaspartate)
<i>Product name:</i>	Signifor
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
<i>Dose form:</i>	Solution for injection
<i>Strengths:</i>	300 µg/1 mL, 600 µg/1 mL and 900 µg/1 mL
<i>Container:</i>	Glass ampoules
<i>Pack sizes:</i>	Cartons containing 6, 30 and 60 ampoules
<i>Approved therapeutic use:</i>	<i>The treatment of patients with Cushing's disease for whom medical therapy is appropriate</i>
<i>Route of administration:</i>	Subcutaneous injection
<i>Dosage:</i>	300 µg to 900 µg twice a day.
<i>ARTG numbers:</i>	201484, 201485, 201486

Product background

Novartis Pharmaceuticals Australia seeks registration of the new chemical entity pasireotide (as diaspartate), which is a novel cyclohexapeptide containing the amino acids L-lysine, D-tryptophan, L-phenylglycine, aminoethylcarbonyl-L-hydroxyproline, L-phenylalanine and O-benzyl-L-tyrosine. It will be formulated as single dose solutions for injection containing 300 µg/1 mL, 600 µg/1 mL and 900 µg/1 mL of pasireotide. The proposed product was granted orphan drug status by the TGA in 2011.

Pasireotide is a somatostatin analogue and exerts its pharmacological activity by binding to four of the five known somatostatin receptors (SSTR) that are found in large numbers in the tumour cells of the pituitary gland. Pasireotide binds to each of these receptors and blocks the release of adrenocorticotrophin (ACTH). This in turn results in the reduction of cortisol levels, thereby helping to relieve the symptoms associated with Cushing's disease.

The proposed product is indicated for:

the treatment of patients with Cushing's disease for whom medical therapy is appropriate.

Regulatory status

The product received initial ARTG Registration on 1 November 2013

Applications for Signifor have been submitted or approved in several jurisdictions (listed in Table 1).

Table 1: Overseas registration status

Country/Region	Tradename	Submitted	Approved	Approved Indication
EU	Signifor	01-Oct-2010	24-Apr-2012	Signifor is indicated for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.
USA	Signifor	17-Feb-2012	17-Dec-2012	Signifor is a somatostatin analog indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.
Canada	Signifor	27-Jan-2011	~Sep-2013	
New Zealand		TBD		
Switzerland	Signifor	29-Nov-2010	02-Nov-2012	Treatment of patients with Cushing's disease if all non-drug therapy alternatives according to current standards have been exploited.

The EMA approved pasireotide on 24 April 2012, the FDA on 14 December 2012 and Switzerland on the 02 November 2012.

The FDA and EMA approved indications differ slightly from the proposed Australian indication (Table 2). The FDA and EMA approved indications restricts the use of the drug to adult patients who are not candidates for surgery.

Table 2: Comparison of indications for Signifor in different jurisdictions

	Indication (or proposed indication)	Approval date
Australia	<i>Treatment of patients with Cushing's disease for whom medical therapy is appropriate.</i>	
EU	<i>Signifor is indicated for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed'</i>	24 April 2012
USA	<i>SIGNIFOR is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.</i>	14 December 2012
Switzerland	<i>Treatment of patients with Cushing's disease if all non-drug therapy alternatives according to current standards have been exploited.</i>	2 September 2012

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

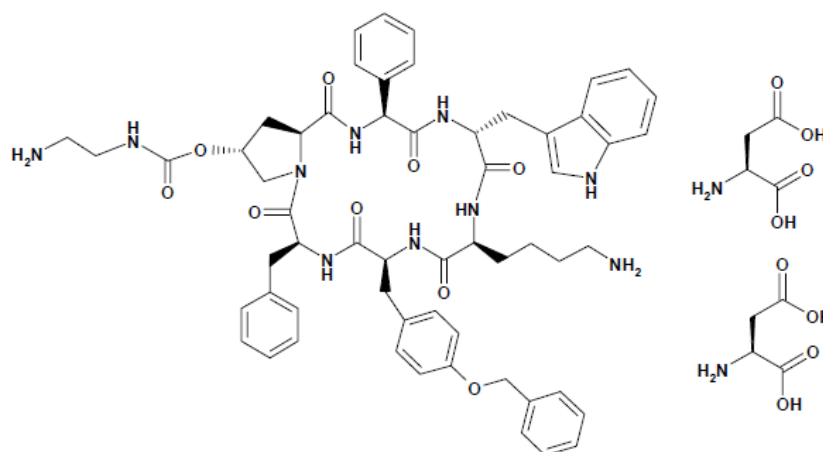
II. Quality findings

Drug substance (active ingredient)

Structure

The drug substance has the following structure:

Figure 1: Structure of pasireotide (as diaspartate)



It is synthesised via a sequence of coupling reactions and deprotection steps using a solid phase peptide (Merrifield) synthetic route. After chromatographic purification, the diaspartate salt is formed by ion-exchange with L-aspartic acid, lyophilised and ultimately obtained as a white to slightly greyish powder.

Pasireotide contains seven chiral centres but is produced as a single stereoisomer of known absolute configuration. The drug substance is insoluble in n-octanol and

acetonitrile, very slightly soluble in acetone and ethanol, sparingly soluble in methanol and freely soluble in water (>10% w/v).

The proposed specifications include tests and limits for identity, related substances, residual solvents, assay and other relevant chemical and physical properties of the drug substance. Detailed information on impurities was provided. Impurity limits are in line with the Ph. Eur. General monograph for substances for pharmaceutical use, criteria applicable to synthetic peptides. The specification limits for the impurities were also justified by toxicology studies and found safe. All of these are adequately controlled.

Adequate method details were provided for the test methods used and appropriate validation data have been submitted in support of the test procedures.

Stability data have been generated under stressed and accelerated conditions that support the proposed retest period of five years when the drug substance is stored between -15°C and -25°C. Photostability studies have shown that the drug substance is light sensitive.

Drug product

The proposed products are sterile water for injection solutions. Each strength of the drug product contains the same amounts of the same three excipients (in 1 mL solutions) whose purpose is to either control the pH (sodium hydroxide), the tonicity (mannitol) or the buffering capacity (tartaric acid) of the solution. The products are manufactured using a standard process comprising: compounding; filtration; filling and terminal sterilisation.

The proposed specifications included tests and limits for: the identity of the drug substance, pH, extractable volume, sub-visible particulate matter, degradation products, assay and other relevant chemical and physical properties of the drug product. The acceptability of the sterility and bacterial endotoxins tests have been considered separately.

The analytical procedures used in the product specifications were adequately described and were supported by appropriate validation data.

Stability data were provided that support the proposed shelf life for the product of 24 months when it is stored below 25°C and protected from light.

Biopharmaceutics

The product is to be administered by subcutaneous (sc) injection. Clinical studies have shown that in healthy volunteers (HV) pasireotide demonstrates approximately linear pharmacokinetics (PK) for a wide dose range from 2.5 µg to 1500 µg. In Cushing's disease patients, pasireotide demonstrates a linear dose-exposure relationship in a dose range from 300 µg to 1200 µg. In HV, pasireotide is rapidly absorbed and peak plasma concentration is reached within a T_{max} of 0.25-0.5 hours. C_{max} and AUC are approximately dose-proportional following administration of single and multiple doses. Based on the accumulation ratios of AUC, the calculated effective half-life ($t_{1/2}$) in HV was approximately 12 hours (on average between 10 and 13 hours for 50, 200 and 600 µg once daily (qd) doses).

Pasireotide has low passive permeability and was shown to be metabolically stable in human liver and kidney microsomes. In HV, pasireotide in its unchanged form is the predominant form found in plasma, urine and faeces. Pasireotide is eliminated mainly via hepatic clearance (biliary excretion) with a small contribution of the renal route.

In the original submission a justification was supplied for not conducting an absolute bioavailability study. It was argued that, on the basis of the physico-chemical properties of the drug substance and an absolute bioavailability study in rats (which demonstrated

100% bioavailability of the product following sc administration), that it was likely that the drug product would be close to 100% bioavailable after sc injection in humans.

Advisory committee considerations

The Pharmaceutical Sub-Committee (PSC) of the ACPM considered this argument and was concerned by the poor agreement between the results from human mass balance study and the PK parameters of the drug substance derived from the population PK (PopPK) study. They recommended that the company should: quantify the percentage of the dose that was recovered as metabolites in the human recovery study; reconcile the expected recovery as predicted by their PK model with that actually observed in the mass balance study in humans and provide an absolute bioavailability study.

The company has responded to these issues but as the response is clinical in nature no evaluation of the response was conducted by the Pharmaceutical Chemistry Section.

Quality summary and conclusions

Approval is recommended with respect to chemistry and quality control.

The ACPM's attention is drawn to the issues raised by the PSC regarding the PopPK analysis and the company's response to these issues.

III. Nonclinical findings

Introduction

Novartis Pharmaceuticals Australia Pty Ltd has applied to register pasireotide (as diaspартate), Signifor, a new chemical entity for the treatment of Cushing's disease in adults. Treatment involves twice daily sc injection. The maximum recommended human dose is 900 µg/day BD.

The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were conducted under Good Laboratory Practice (GLP) conditions with the exception of one on in vitro cardiovascular safety (involving experiments with isolated rabbit Purkinje fibres). The relevant EU guideline (CHMP/ICH/423/02) specifies that such a study should be conducted according to GLP. However, the study was well documented nevertheless, and this is considered to be only a minor deficiency.

Pharmacology

Primary pharmacology

Pasireotide is a cyclohexapeptide somatostatin analogue. Pasireotide was shown to bind with high affinity to four of the five human somatostatin (hsst) receptor subtypes: in experiments measuring inhibition of radiolabelled somatostatin binding to recombinant receptors, half maximal inhibitory concentration (IC₅₀) values for pasireotide were 9.3 nM at hsst1, 1.0 nM at hsst2, 1.5 nM at hsst3 and 0.16 nM at hsst5 (compared with >100 nM at hsst4). This stands in contrast to the existing somatostatin analogues, octreotide (Sandostatin) and lanreotide (Somatuline), which primarily target the hsst2 subtype (with respective IC₅₀ values of 0.38 and 0.54 nM); these agents have 39 and 106 times, respectively, lower affinity for hsst5 than pasireotide. Somatostatin receptor agonist activity was demonstrated for pasireotide in cell-based functional experiments, with

forskolin-stimulated cAMP accumulation inhibited by pasireotide at nanomolar or subnanomolar concentrations in cells expressing recombinant *hsst1*, *hsst2*, *hsst3* and *hsst5*; no agonist activity was observed with pasireotide at *hsst4*. In vivo, pasireotide (3 or 10 µg/kg in vitro) was shown to inhibit corticotrophin releasing hormone-induced ACTH and corticosterone secretion in rats more strongly than octreotide.

Of relevance to the proposed indication, in vitro studies have shown that corticotroph tumour cells from Cushing's disease patients express high levels of *hsst5* (that is, the subtype most potently targeted by pasireotide), whereas the other four somatostatin receptor subtypes are either not expressed or are expressed at a significantly lower level (Batista et al., 2006¹). While *hsst2* receptors on corticotroph cells are down-regulated in the presence of high levels of glucocorticoids, *hsst5* receptors are not affected (Hofland et al., 2005²; van der Hoek, 2004³).

Secondary pharmacodynamics and safety pharmacology

Consistent with somatostatin activity, inhibition of growth hormone (GH) release by pasireotide was shown in vitro in rat pituitary cells and in vivo in rats and monkeys after sc administration. Greater potency was evident for pasireotide compared with octreotide in vitro (greater than three-fold). Pasireotide inhibited basal GH in rats with roughly similar activity as octreotide, but with a much longer duration of action. Inhibition of GH in cynomolgus monkeys was stronger and longer lasting with pasireotide compared to octreotide, while activity in rhesus monkeys was comparable for the two drugs. Pasireotide caused a greater and more sustained reduction in plasma IGF-1 levels compared to octreotide in both rats and (cynomolgus) monkeys.

Compared with octreotide, pasireotide was a much more potent inhibitor of insulin secretion (> 100 times), and a much weaker inhibitor of glucagon (44 times) and gastrin (37 times) secretion, in rats. Consistent with this stronger inhibition of insulin compared with glucagon secretion, pasireotide caused a marked transient increase in plasma glucose in the species (while octreotide caused no increase); this effect lessened with repeated dosing. Decreased insulin, glucagon and glucose were seen in rhesus monkeys given pasireotide (and more prominently with octreotide), but no notable effects on insulin, glucagon or glucose were seen with pasireotide (or octreotide) in cynomolgus monkeys.

In screening assays against a panel of 69 G-protein coupled receptors, transporters and ion channels, the most potent inhibition of ligand binding seen with pasireotide was at the κ-opiate (K_i, 41 nM), ghrelin (0.15 µM), 5-HT_{1A} (0.31 µM) and µ-opiate (0.42 µM) receptors (human); twelve other targets had K_i values of 1–10 µM. The lowest K_i value is more than 256 times higher than the IC₅₀ observed at *hsst5* (and 4.4–41 times higher compared with the IC₅₀ values at *hsst1–3*), and more than 12 times higher than the peak free plasma concentration of pasireotide expected in patients at the maximum recommended human dose (approximately 3.3 nM⁴). Clinical relevance is further reduced by the demonstration of very limited entry of the drug into the central nervous system (CNS) in rats.

¹ Batista D.L., Zhang X., Gejman R., Ansell P.J., Zhou Y., Johnson S.A., Swearingen B., Hedley-Whyte E.T., Stratakis C.A and Klibanski A. 2006. The effects of SOM230 on cell proliferation and adrenocorticotropin secretion in human corticotroph pituitary adenomas. *J. Clin. Endocrinol. Metab.* 91:4482–4488.

² Hofland L.J., van der Hoek J., Feelders R., van Aken M.O., van Koetsveld P.M., Waaijers M., Sprij-Mooij D., Bruns C., Weckbecker G., de Herder W.W., Beckers A. and Lamberts S.W. 2005. The multi-ligand somatostatin analogue SOM230 inhibits ACTH secretion by cultured human corticotroph adenomas via somatostatin receptor type 5. *Eur. J. Endocrinol.* 152:645–654.

³ van der Hoek J., Lamberts S.W. and Hofland L.J. 2004. The role of somatostatin analogs in Cushing's disease. *Pituitary.* 7:257–264

⁴ Based on a steady state plasma C_{max} of 29.0 ng/mL at 900 µg BD (Clinical Study CSOM230B2113), a molecular weight of 1047.21, and assuming plasma protein binding of 88% (Study DMPK(CH) R99-2082).

Specialised safety pharmacology studies covered the CNS, cardiovascular and respiratory systems. CNS function was unaffected in mice at ≤ 4 mg/kg sc (estimated relative exposure based on C_{max} , > 100); ataxia, slightly decreased locomotor activity, decreased grip strength, hyposensitivity to sound, ptosis, loss of righting reflex (from 15 minutes post-dose and dissipating by six hours post-dose) and decreased body temperature (one hour post-dose) were observed at 15 mg/kg sc. Pasireotide was shown to only weakly inhibit the hERG K⁺ channel ($IC_{50} > 30$ μ M; > 1000 times higher than the clinical C_{max} at the maximum recommended human dose). The maximum rate of depolarisation (V_{max}) was reduced with pasireotide at 73 μ M in experiments with isolated rabbit Purkinje fibres; no effect on action potential parameters was observed at a nominal concentration of 30 μ M (actual concentration, approximately 10–22 μ M, reflecting absorption of the compound to the perfusion system). Cardiovascular parameters (blood pressure (BP), heart rate and ECG) were unaffected in monkeys at ≤ 1.6 mg/kg sc (estimated relative exposure based on C_{max} , 56), and no treatment-related effects on respiratory parameters were observed in rats at ≤ 4 mg/kg sc (estimated relative exposure based on C_{max} , > 16).

Pharmacokinetics

Absorption of pasireotide after sc injection was relatively rapid in all species (mouse, rat, rabbit, monkey and human), with peak plasma concentrations typically reached within 0.25–2 hours. Pasireotide was shown to be well absorbed in rats and monkeys (84–100%) after sc administration; bioavailability was estimated to be complete in animals and reported to be complete in humans too. Plasma terminal $t_{1/2}$ was much shorter in rats (1.3 hours) than in monkeys (56 hours) and humans (12 hours). Plasma AUC values were generally dose-proportional in all species. Exposure was higher in male mice and rats compared with females; no consistent sex difference was evident in monkeys.

Plasma protein binding by pasireotide was moderate to high and similar in humans (88%), rats and dogs (93–94%) and independent of concentration. Distribution into red blood cells was low (assessed in rats, dogs and humans). Tissue distribution of radioactivity after IV injection of ¹⁴C-pasireotide was rapid and wide in rats, with highest levels of radioactivity found in the kidney, lymph nodes, blood vessel wall, liver and ear; penetration of the blood-brain barrier was minimal (the peak concentration of radioactivity in brain being 52 times lower compared with blood). The systemic distribution profile was similar with sc administration. Steady-state volume of distribution was lower in the rat (0.29 L/kg) than in the monkey (1.1 L/kg) and humans (1.39 L/kg).

Pasireotide was minimally metabolised in rats, monkeys and humans after sc administration. Due to their low abundance, metabolites formed in vivo were generally not structurally characterised. The drug was also shown to be highly metabolically stable in vitro in experiments with rat, monkey and human liver microsomes, rat hepatocytes and human kidney microsomes. Two metabolites, P24 (formed by mono-oxidation of the tryptophan moiety) and P30 (representing deamination of the lysine moiety), were observed at low levels following incubation of pasireotide with human liver microsomes; P30 was also identified as a circulating metabolite in monkeys in vivo. Another minor metabolite (P2; not structurally characterised) was found to be formed following incubation with monkey liver microsomes. CYP3A4 and CYP3A5 were identified as the CYP isozymes primarily involved in the metabolism of pasireotide, generating metabolites P24 and P30, respectively. Excretion of ¹⁴C-pasireotide-derived radioactivity was predominantly via the faeces in all species (rats, monkeys and humans); renal elimination was 6–9% of the dose.

The PK profiles of pasireotide in the laboratory animal species used in the pivotal repeat dose toxicity studies (rats and monkeys) are sufficiently similar to that in humans to allow them to serve as appropriate models for pasireotide toxicity in humans.

Pharmacokinetic drug interactions

Pasireotide showed inhibitory activity against CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5. CYPs 2C9 and 2D6 were the isozymes most sensitive to inhibition, with IC50 values approximately 5 µM for both; IC50 values for the other CYPs ranged from 10 to > 100 µM. Pasireotide was also shown to be able to inhibit UGT1A1 (IC50 value, 59–100 µM). These IC50 values are > 180 times higher the clinical C_{max}, and no significant CYP or UGT1A1 inhibition is predicted in patients.

Experiments in Caco-2 cells indicated that pasireotide was a substrate of P-glycoprotein (but also to be a low permeable compound). Pasireotide was shown not to be a substrate of BCRP (breast cancer resistance protein), OCT1, OATP1B1, OATP1B3 or OATP2B1, and the drug (≤ 1 µM) did not inhibit OATP1B1 or OATP1B3.

Pasireotide inhibited P-glycoprotein with an IC50 of 0.85 µM, and BCRP, MRP2 (multidrug resistance-associated protein 2) and BSEP (bile salt export pump) each with an IC50 of approximately 10 µM in experiments with inside-out vesicles. The IC50 values being more than 30 and 360 times the clinical C_{max}, no significant inhibition is expected in patients.

The drug (≤ 1 µM) did not induce CYPs 1A1, 1A2, 1B1, 2B6, 2C8, 2C19, 3A, 2J2, or P-glycoprotein or MRP2 in cultured human hepatocytes. Increases in CYP2C9 mRNA (2.8–5.0 fold at 5–100 nM) and UGT1A1 activity (2.15 fold at 100 nM) were observed in one third of hepatocyte cultures (without corresponding increases in CYP2C9 activity or UGT1A1 mRNA in any of the three cultures). Considering the data overall, PK drug interactions due to enzyme induction by pasireotide are not predicted.

Peak and overall exposure to orally administered cyclosporin A was decreased in dogs co-treated with pasireotide sc (by 46–47%); octreotide had a similar effect.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted in mice and rats using the clinical (sc) route. Animals of both sexes were used, and the observation period was 14 days, in accordance with the EU guideline on single-dose toxicity (3BS1a). No deaths occurred in either species up to the maximum dose tested, 30 mg/kg. Adjusted for body surface area, this dose is approximately 75–150 times higher than the maximum recommended human dose per day (900 µg BD; assuming 50 kg patient body weight (BW)). Notable effects were limited to injection site sores (both species) and BW loss (rats). Systemic tissues displayed no gross abnormalities.

Repeat-dose toxicity

Studies of up to four weeks duration were conducted in mice, six months in rats, three days in dogs and nine months in monkeys using the clinical (sc) route. The duration of the pivotal studies, the species used (rats and monkeys), group sizes and the use of both sexes were consistent with The International Conference on Harmonisation (ICH) guidelines. Dosing in the pivotal studies was once per day, which is less frequent than that proposed clinically (twice per day), but this is not considered to impact the validity of the studies and does allow for higher peak drug concentrations to be examined; twice daily sc dosing was used in studies of up to four weeks duration in rats and dogs. Studies by the Oral (PO) and intravenous (IV) routes in rats and dogs (up to two or four weeks duration) and involving intramuscular (IM) administration of a long-acting release formulation (once monthly administration for up to six months) in rats were also submitted, but are of

limited usefulness/relevance to the current application. The assessment focuses on the sc studies.

Relative exposure

Exposure ratios have been calculated in Table 3 below based on animal:human plasma AUC_{0-24 h} values for pasireotide. Low multiples of the clinical exposure were obtained in the pivotal rat study, while multiples were very high in the pivotal monkey study, and moderate multiples were achieved in the two rodent carcinogenicity studies.

Table 3: Relative exposure in selected repeat-dose toxicity and carcinogenicity studies

Species		Study duration	Dose (mg/kg/day); sc	AUC _{0-24 h} (ng·h/mL)		Exposure ratio#	
				♂	♀	♂	♀
Mouse	(CB6F1)	4 weeks [0570087]	10	29791	22432	102	77
			20	57715	36391	198	125
			30	66309	42333	228	145
	(CB6F1/ TgrasH2)	4 weeks [0470037]	1	4561	948	16	3.3
			2.5	3773	3027	13	10
			5	19345	10485	66	36
			10	55693	42181	191	145
		6 months [carcinogenicity; 0470111]	0.5	755a	605a	2.6	2.1
			1	1509a	1211a	5	4
	Rat (Wistar Han)	4 weeks [0170115]	0.008b	32.2c	16.8c	0.1	0.06
0.08b			306c	143c	1.1	0.5	
0.8b			3842c	1116c	13	3.8	
0.8			2329	876	8	3.0	
6 months [pivotal; 0210056]			0.008	19.4	-	0.07	-
			0.024	95.9	44.3	0.3	0.15
			0.08	-	143	-	0.5
			0.24	748	560	2.6	1.9
2 years [carcinogenicity; 0670694]		0.01	56.2	28.8	0.2	0.1	
		0.05	347	363	1.2	1.2	

Species	Study duration	Dose (mg/kg/day); sc	AUC _{0-24 h} (ng·h/mL)		Exposure ratio#	
			♂	♀	♂	♀
		0.3	3980	1900	14	7
Monkey (Cynomolgus)	9 months [pivotal; 0270130]	0.4	3707		13	
		1.6	13645		47	
		3.2	28888		99	
Human (healthy volunteers)	steady state [CSOM230B2113]	[900 µg BD]	291.2d		-	

= animal:human plasma AUC_{0-24h}; ^a = estimated based on data from Study 0470037 due to limited toxicokinetic sampling in the main study; ^b = BD administration (~6 h) apart; ^c = reported AUC_{0-6h} value has been multiplied by 2 to reflect twice daily dosing; ^d = reported AUC_{0-12h} value has been multiplied by 2 to reflect twice daily dosing

Major targets

The major targets for pasireotide were the pituitary, bone, bone marrow, spleen, thymus, thyroid, female reproductive tract and sc injection site, with effects on the gastrointestinal (GI) tract also seen.

Pasireotide was better tolerated in monkeys than rats. The dog was found to be particularly sensitive to pasireotide, with severe vomiting and diarrhoea seen at all dose levels in a pilot study in the species (≥ 0.07 mg/kg/day sc), prompting discontinuation of dosing within one to three days and the selection of the monkey as the non-rodent species. In contrast, there were no GI findings in rodents (notably even at hundreds of times the clinical exposure level in mice). Monkeys showed no clinical signs of GI toxicity, although distension of the large intestine with firm faecal material and the presence of proteinaceous material in the crypts of the mucosa of the caecum and colon were seen at ≥ 1.6 mg/kg/day sc in the four week and nine month studies (relative exposure, ≥ 47); distension of the large intestine with firm faecal material was also seen in one of eight monkeys treated at 0.4 mg/kg/day sc for nine months (relative exposure, 13). These findings are consistent with the recognised effect of somatostatin to inhibit GI tract secretions and motility.

Substantial inhibition of BW gain or BW loss were routinely seen in studies in rodents, including at all dose levels in male rats (≥ 0.008 mg/kg/day sc; relative exposure, ≥ 0.07) and in female rats at 0.24 mg/kg/day sc (relative exposure, 1.9) in the pivotal six month study. BW gain was unaffected in monkeys in the pivotal nine month study (≤ 3.2 mg/kg/day sc; relative exposure, ≤ 99). Pharmacologically mediated reductions in serum GH and/or IGF-1 (which is directly responsive to GH) were shown in the two pivotal species. Consistent with inhibition of GH secretion from somatotrophs, decreased cytoplasmic volume of the acidophilic cells of the pars distalis was seen in mice (at ≥ 2.5 mg/kg/day sc relative exposure, ≥ 10) and rats (at ≥ 0.024 mg/kg/day sc in males in the pivotal study; relative exposure, ≥ 0.3). The greater sensitivity to growth suppression and pituitary changes evident with pasireotide in male compared with female rats can be attributed to notable differences in GH and somatostatin regulation recognised between

the sexes in the species (Wehrenberg and Giustina, 1992⁵). Increased acidophilia of the pars distalis of the pituitary was observed in both sexes at all doses in the pivotal monkey study (≥ 0.4 mg/kg/day sc; relative exposure, ≥ 13). Reversibility of the pituitary changes was demonstrated in rats and monkeys.

In mice, pasireotide minimally decreased primary spongiosa in the metaphysis below the growth plate of the tibia and femur with treatment at ≥ 10 mg/kg/day sc for four weeks (relative exposure, ≥ 77); a NOEL (no observed effect level) of 2.5 mg/kg/day sc (relative exposure, 13) for skeletal effects is established in the mouse carcinogenicity study. In rats, decreased primary spongiosa of the femur/tibia/sternum was observed in a six month study conducted with a long-acting release formulation of pasireotide (administered IM), and metaphyseal trabecular atrophy of the femur and sternum was observed with treatment at 0.8 mg/kg/day sc for four weeks. However, bone formation was seen to be unaffected in the pivotal six month sc rat study and in the rat carcinogenicity study (relative exposure, ≤ 14). No skeletal changes were observed in monkeys (relative exposure, ≤ 99 in the pivotal nine month study).

Pasireotide decreased bone marrow cellularity in male rats at ≥ 0.04 mg/kg/day sc in a two week study (estimated relative exposure, 0.5) and in monkeys (both sexes) at ≥ 1.6 mg/kg/day sc in a four week study (relative exposure, ≥ 24). Red blood cell count, haemoglobin and haematocrit were reduced in mice treated with pasireotide at 30 mg/kg/day sc for four weeks (relative exposure, ≥ 145). Lymphoid depletion and reduced haematopoiesis were observed in the spleen of treated rats (including in males in the pivotal study at 0.24 mg/kg/day sc; relative exposure, 2.6). Thymic lymphoid atrophy/depletion was observed in short-term studies in rats (≥ 0.8 mg/kg/day sc for four weeks); decreased BW relative thymus weight, without accompanying histopathological findings, was observed in mice (≥ 10 mg/kg/day sc) and in other non-pivotal studies in rats. Treatment with pasireotide reduced BW relative thyroid weight and caused microscopic thyroid changes (attenuation of the follicular epithelium; small follicles with foamy cytoplasm) in monkeys. In the pivotal nine month monkey study, histopathological changes in the thyroid (small follicles) were observed at ≥ 1.6 mg/kg/day sc in males (relative exposure, 47) and at all dose levels in females (≥ 0.4 mg/kg/day sc; relative exposure, 13). The inhibitory effects on haematopoietic and lymphoid organs and the thyroid observed with pasireotide are considered to be related to the drug's primary pharmacological action (either directly or indirectly). Somatostatin inhibits TSH (thyroid stimulating hormone) release; binding to somatostatin receptors on lymphocytes, monocytes and haematopoietic precursors leads to inhibition of cell proliferation; and stimulation of erythropoiesis will be reduced with decreased IGF-1.

Prolongation of the oestrus cycle was evident in rats treated at ≥ 0.08 mg/kg/day sc in the pivotal six month study (relative exposure, ≥ 0.5), together with a decrease in the number of corpora lutea and findings of vaginal mucosal hyperplasia or hypertrophy with mucification, and, at 0.24 mg/kg/day sc, an increased incidence of (oestrus cycle-related) dilatation of the uterus. Prolongation of the oestrus cycle was also observed in rats treated at 4 mg/kg/day sc for two weeks, and ovarian interstitial cell hyperplasia was seen at 0.8 mg/kg/day sc in rats treated for 4 weeks. The corpora lutea of mice treated at ≥ 20 mg/kg/day sc for 4 weeks (relative exposure, ≥ 125) were decreased in size and number, accompanied by uterine atrophy. No effects on oestrus cycling or on female reproductive tract tissues were observed in monkeys (relative exposure, ≤ 99 in the pivotal

⁵ Wehrenberg W.B. and Giustina A. 1992. Basic counterpoint: mechanisms and pathways of gonadal steroid modulation of growth hormone secretion. *Endocr. Rev.* **13**:299-308.

nine month study). The effects in rodents are considered to reflect the pharmacological reduction in serum IGF-1 levels.

Reddening of the ears, feet and tail and swelling of the muzzle, ears and feet were observed in two and four week sc studies in rats, but not in the pivotal rat study. There were no similar findings in sc studies in monkeys (relative exposure, ≤ 99 based on AUC — and even higher based on C_{max} — in the pivotal study), although redness of the face and other body areas and swelling of eyelids were seen in monkeys treated IV. The oedema and hyperaemia is consistent with the known vasodilator activity of somatostatin (mediated by release of nitric oxide from endothelial cells).

Locally, sc injection of pasireotide caused irritation and degeneration of the adjacent skeletal muscle, but was overall fairly well tolerated in the laboratory animal species. The highest strengths of pasireotide tested in rats and monkeys were 4.4 and 14 times higher than the maximum proposed clinical strength (900 $\mu\text{g}/\text{mL}$).

Genotoxicity

The potential genotoxicity of pasireotide was investigated in the standard battery of tests; a bacterial reverse mutation assay, an in vitro chromosomal aberration assay in human lymphocytes, and a rat bone marrow micronucleus assay. The conduct of the studies was in accordance with ICH guidelines. Concentrations/doses were appropriate (limited by cytotoxicity, mitotic suppression and/or solubility in vitro and producing bone marrow suppression at the high-dose level used in vivo), a suitable set of *S. typhimurium* strains was used in the bacterial mutagenicity assay, and the assays were appropriately validated. All assays returned negative results.

Carcinogenicity

The carcinogenic potential of pasireotide by the sc route was investigated in a six month study in transgenic mice (Tg rasH2) and a two year study in rats. Group sizes were appropriate and suitable dose levels were selected, with substantial inhibition of BW gain observed in male and female mice and male rats at all doses, as well as at the high-dose level in female rats. The inhibition of BW gain exceeded 10% (a level commonly used to define the maximum tolerated dose), but survival was not affected. Dosing was once per day (compared with twice daily in patients), but this is not considered to impact the validity of the studies.

No treatment-related increase in tumour incidence was observed in transgenic mice (≤ 2.5 mg/kg/day; estimated relative exposure based on plasma AUC, 13 in males and 10 in females). In rats, treatment at the high-dose level of 0.3 mg/kg/day was associated with the development of injection site fibromas (observed in three of 50 animals). Female rats showed no injection site fibromas, and no treatment-related increase in systemic tumours was observed in either sex (relative exposure based on AUC, 14 in males and seven in females). The development of injection site tumours is consistent with a response to continuous irritation/inflammation at the repeatedly injected site, and the dose at which they occurred is more than 16 times the clinical dose (on a mg/kg basis). Similar findings have been observed in rodents with lanreotide and octreotide, and they are not considered to indicate a carcinogenic potential in humans. In addition, the draft Product Information (PI) document contains a recommendation to avoid administration at previous injection sites that show signs of inflammation or irritation.

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages (fertility, early embryonic development, embryofetal development, and pre and post-natal development). Numbers of animals and the timing/duration of treatment were appropriate. Administration was by the sc route. An in vitro study using rat whole embryo cultures was also submitted.

Table 4: Relative exposure

Species	Study	Dose; sc		AUC _{0-24h} (ng·h/mL)	Exposure ratio [#]	
		mg/kg/day	mg/m ² /day		based on AUC	based on mg/m ²
Rat (Wistar Han)	Fertility	0.1	0.6	–	–	0.5
		1	6	–	–	5
		10	60	–	–	51
	Embryofetal development	1	–	4930	17	–
		5	–	25594	88	–
		10	–	42179	145	–
	Pre/postnatal development	2	12	–	–	10
		5	30	–	–	25
		10	60	–	–	51
Rabbit (NZW)	Embryofetal development	0.05	–	114	0.4	–
		1	–	1906	6.5	–
		5	–	11766	40	–
Human (HV)	steady-state	[900 µg BD]	1.188	291.2	–	–

[#] = for studies that did not include toxicokinetic analyses, exposure ratios are calculated based on animal:human body surface area-adjusted doses, using mg/kg to mg/m² conversion factors of 6 for rats and 33 for humans (50 kg)

High multiples of the anticipated clinical exposure were achieved at the highest dose levels tested. 14C-Pasireotide-derived radioactivity was shown to cross the placenta at low levels in rats (fetal AUC, approximately 7% of the maternal plasma AUC); the drug was also shown to cross the placenta in rabbits. Excretion of pasireotide in milk was demonstrated in lactating rats (milk:plasma AUC for 14C-pasireotide-derived radioactivity, 27%).

Fertility was seen to be unaffected in male rats at ≤ 10 mg/kg/day sc (estimated relative exposure, 51). In female rats, the fertility index was decreased at 10 mg/kg/day, and oestrus cycling was disrupted (prolonged/acyclic) and corpora lutea were decreased at doses ≥ 1 mg/kg/day (estimated relative exposure, ≥ 5); the number of implantations and viable fetuses were reduced at all dose levels tested (≥ 0.1 mg/kg/day; estimated relative exposure, ≥ 0.5).

In rats, treatment at 10 mg/kg/day (relative exposure, 145) increased post-implantation loss, decreased mean fetal weight, increased the incidence of fetuses with malrotated limbs and inhibited ossification of the hindpaw phalanx; this dose was maternotoxic. The NOEL for embryofetal development in the rat was 5 mg/kg/day (relative exposure, 88). In rabbits, treatment at ≥ 1 mg/kg/day (relative exposure, ≥ 6.5 ; maternotoxic) increased post-implantation loss, decreased fetal weight, and impaired ossification (forepaw phalanx); abortions and further impairment of ossification (talus) were observed at 5 mg/kg/day (relative exposure, 40). The NOEL for embryofetal development in the rabbit is 0.05 mg/kg/day (relative exposure, 0.4). The effects on embryofetal development observed in rats and rabbits are considered most likely to be secondary to maternotoxicity (that is, severe effects on BW), rather than to reflect a direct toxic effect on the fetus.

In a pre/postnatal development study in rat, pasireotide decreased pup birth weight and pre-weaning BW gain, and delayed pinna unfolding, at all dose levels (≥ 2 mg/kg/day; estimated relative exposure, ≥ 10), occurring in conjunction with maternal toxicity. No NOEL for adverse effects on pre/postnatal development was established.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3. This category is considered appropriate given the adverse effects on embryofetal development in rats and rabbits seen with pasireotide here.

Immunotoxicity

In a specialised four week immunotoxicity study in rats, pasireotide decreased splenic lymphocyte counts in males (≥ 0.24 mg/kg/day; all sub-populations) and caused bone marrow hypocellularity in both sexes (≥ 0.24 mg/kg/day in males; 0.8 mg/kg/day in females), but had no effect on anti-KLH IgM or IgG responses (≤ 0.8 mg/kg/day; estimated relative exposure, ≤ 3.0 in females and ≤ 8 in males).

Local tolerance and phototoxicity

Local tolerance tests (in rabbits) were adequately conducted and revealed no significant dermal irritation with pasireotide and mild ocular irritation. No phototoxic potential was found for pasireotide in vitro in the 3T3 Neutral Red uptake assay.

Impurities

The proposed specifications for related substances as impurities/degradants in the drug substance/product do not exceed the applicable qualification threshold for organic impurities in peptides obtained by chemical synthesis (that is, 1.0%; *Ph. Eur.* monograph 2034).

Paediatric use

Pasireotide is not proposed for paediatric use and no specific studies in juvenile animals were submitted. Growth retardation (pharmacologically mediated) would be expected.

Nonclinical summary and conclusions

Summary

- Novartis Pharmaceuticals Australia has applied to register a new chemical entity, pasireotide diaspertate (Signifor) for the treatment of Cushing's disease in adults.

- The nonclinical dossier was of high quality. All pivotal safety-related studies, except one relating to the *in vitro* assessment of cardiovascular safety, were conducted according to GLP.
- Pasireotide was shown to bind to four of the five human somatostatin receptor subtypes with nanomolar or (in the case of *hsst5*) subnanomolar affinity. Somatostatin receptor agonist activity was demonstrated *in vitro* in cell-based functional experiments, and inhibition of ACTH and corticosterone secretion was shown *in vivo* in rats.
- Receptor screening assays identified the κ -opiate, ghrelin, 5-HT_{1A}, and μ -opiate receptors as the most potent secondary targets of pasireotide.
- Safety pharmacology studies covered the CNS, cardiovascular and respiratory systems. Pasireotide was only a weak inhibitor of the hERG K⁺ channel, and affected CNS function at only very high exposure levels in mice. The drug did not affect cardiovascular or respiratory function in animals *in-vivo*.
- Bioavailability was estimated to be complete following *sc* injection in laboratory animal species. Tissue distribution of radioactivity following IV injection of ¹⁴C-pasireotide was rapid and wide in the rat; penetration of the blood-brain barrier was low. Plasma protein binding was moderate to high in humans and animals. Pasireotide was minimally metabolised *in vivo* and *in vitro*. Excretion was predominantly via the faecal route.
- In single-dose toxicity studies in rodents, *sc* injection of a high multiple of the maximum recommended human dose produced no deaths and no gross tissue changes.
- Pivotal repeat-dose toxicity studies were conducted by the *sc* route in rats (six months) and monkeys (nine months). The major effects were on BW gain, the pituitary, bone, bone marrow, spleen, thymus, thyroid, female reproductive tract and *sc* injection site, with effects on the GI tract also seen.
- Pasireotide was not genotoxic in the standard battery of tests and not carcinogenic in a six month *sc* study in transgenic mice. Injection site tumours (fibromas) were increased in male rats at the highest dose in a two year *sc* carcinogenicity study; there was no similar finding in female rats and no treatment-related increase in systemic tumours.
- Pasireotide impaired female fertility in rats. Adverse effects on embryofetal development were observed in rats and rabbits, albeit in conjunction with maternotoxicity. Pup birth weight and postnatal BW gain were decreased and development delayed in a pre/postnatal development study in rats.
- No functional impact on immune function was observed in rats. The drug was found not to have phototoxic potential in an *in vitro* assay.

Recommendations

The nonclinical dossier contained no major deficiencies.

- Primary pharmacology studies, showing high affinity for a broad range of somatostatin receptor subtypes, and inhibition of ACTH secretion *in vivo*, support the drug's use for the proposed indication.
- No clinically significant off-target activities are predicted from secondary PK studies.
- Major findings in the repeat-dose toxicity studies are identified as representing exaggerated pharmacological effects. A significant difference in sensitivity across

species is evident. Most weight is placed on the studies in monkeys, where the drug was well tolerated at almost 100 times the clinical exposure level in the pivotal (nine month) study. Good local tolerance at the subcutaneous injection site has also been demonstrated.

- Pasireotide is not considered to pose a genotoxic or carcinogenic hazard in patients. The finding of increased injection site tumours (fibromas) in male rats mirrors similar findings for other somatostatin analogues (octreotide and lanreotide), and is not considered to be of clinical relevance.
- Disruption of oestrus cycling and inhibition of ovulation in rats is seen to be pharmacologically mediated. Lesser sensitivity of humans is predicted based on comparisons of findings in the monkey and rat repeat-dose toxicity studies. Adverse effects on embryofetal development in rats and rabbits are considered most likely to have occurred secondary to maternal toxicity.
- There are no nonclinical objections to the registration of Signifor for the proposed indication.
- The Nonclinical Safety Specification of the draft Risk Management Plan (RMP) should be revised

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The submission contained the following clinical information:

- 12 clinical pharmacology studies, including 11 that provided PK data and nine that provided pharmacodynamics (PD) data.
- PopPK analyses for HV and the target population of Cushing's disease patients (modelling reports).
- The report of a single pivotal efficacy/safety Study CSOM230B2305 (referred to hereafter as Study B2305), together with ancillary documents detailing protocol amendments and statistical methodology.
- Four other efficacy/safety studies.
- Three bioanalytical reports validating the immunoassay procedures for analysis of pasireotide (sponsor code SOM230). A lower limit of quantification is described of 30 pg/mL, which equates to 150 pg/mL in study samples. These documents have not been reviewed in detail.
- Population safety reports on glucose metabolism, QT/QTc (cardiac safety), and a hepatic safety report

Paediatric data

The submission did not include paediatric data. The sponsor advises that a relevant product specific waiver was granted by the European Medicines Authority (EMA) on 6 March 2009, on the grounds that the product "does not represent a significant therapeutic benefit over existing treatments". The details pertaining to the waiver were requested of the Sponsor and their response was that given the excellent response rate of

paediatric patients to first-line therapies, the potential of pasireotide to inhibit GH secretion and the very low prevalence of CD in children, it is deemed not feasible to conduct an adequate study to determine the therapeutic benefit and risk of pasireotide in paediatric CD patients for whom medical therapy would be appropriate.

Good clinical practice

The included studies all appear to have complied with the accepted procedures for Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 shows the studies relating to each PK topic.

Table 5: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	
PK in healthy adults	General PK	Single dose	B2101
			B2107
			C2101
	Infusion		B2108
	Multi-dose		B2102
			B2106
			B2107
			B2113
		B2125	
	Bioavailability (mass balance)	B2112	
PK in special populations	Target population §	Multi-dose	B2208
			B2305
	Hepatic impairment		B2114
Population PK analyses	Healthy subjects		Module 5.3.3.5
	Target population		Module 5.3.3.5

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacokinetics

The PK profile of pasireotide has been well characterised, both in HV and the target population, in respect of its intended use by sc injection for patients with Cushing's disease. Rapid and complete absorption with dose proportionality across the proposed therapeutic range, absence of significant interference by metabolites, and major dependence on hepatic excretion have all been established.

Increased exposure in the target population is identified and appears largely due to the covariate of age. This should be made clearer in information on PK in the draft PI.

As discussed above, the data on single dose PK exposure in hepatically impaired patients is accurate as it stands but does not adequately assess the potential for hazardous exposure

with multiple dosing. This has implications for relevant sections of the contraindications, precautions and dosing sections of the draft PI.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 6 shows the studies relating to each PD topic. Note that a number of these studies also appear in Table 5 as many of the Phase I studies include both PK and PD data; also that there are no clinical studies relating to the primary PD action of pasireotide for the purpose of this application, which is its action in suppressing ACTH release from the pituitary, and from pituitary tumour cells in particular. This has been established in in vitro studies.

Table 6: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Secondary Pharmacology	Effect on growth hormone release	B2101
	Effect on glucose homeostasis	B2102
		B2102*
		B2106*
		B2107*
		B2216
	Cardiac repolarisation	B2113
	B2125	
PD Interactions	Metformin, vildagliptin, liraglutide and nateglinide	B2124
Population PD and PK-PD analyses	Target population with pituitary Cushing's disease	Module 5.3.3.5

None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacodynamics

Evidence for the primary PD effects of pasireotide on ACTH and cortisol secretion in patients with pituitary corticotroph tumours rests on in vitro studies not reviewed in this evaluation, and its effectiveness in the Phase III efficacy studies.

Pasireotide has, as described above, a number of secondary PD actions which reflect the widespread inhibitory role of somatostatin in endocrine physiology. Physiological GH secretion is suppressed at a lower dosage threshold than that found for pasireotide's therapeutic action in Cushing's disease.

The lower dosage threshold also observed for pasireotide's secondary PD effect on glucose homeostasis, by comparison with its PD effect on cortisol secretion in Cushing's disease, is of practical importance in relation to safety: it implies that maximal effect on parameters of glucose homeostasis are likely to be seen at any dose within the therapeutic range, so that downward adjustment of dosage would be unlikely to ameliorate hyperglycaemia should this occur as an adverse effect. It is likely that the same applies to the variety of other secondary PD actions assessed in Study B2102, all of which have some potential as the basis for safety issues.

The mechanism for the secondary PD effect on glucose homeostasis has been extremely well-documented in the included studies. The drug PD interaction Study B2124 suggests that oral diabetes therapies which act through the incretin effect are most likely to be

useful in managing hyperglycaemia should this be necessary. The importance of these observations in relation to safety, particularly in long-term use, is discussed below.

Efficacy

Studies providing efficacy data

Study B2305

This was a Phase III, randomised, double-blind study to assess the efficacy and safety of different doses of subcutaneously administered pasireotide over a six month treatment period in patients with newly arising, persistent or recurrent Cushing's disease. It was undertaken between December 2006 and March 2010 at 53 international centres.

The study design undertakes comparison of two dosage levels (600 µg BD and 900 µg BD). Following randomisation to one of these two treatment arms, double-blind treatment was to continue for six months unless a 300 µg dose increment was indicated on the basis of pre-established criteria at the three month assessment. Following this there was a further six month open-label phase. There was no placebo or active control. The sponsor argues that a placebo group would be ethically unacceptable because of the severity of the condition and some of the circumstances of recruitment (for example, failed response to surgery); and that an active control is impractical because there is no alternative approved treatment.

Comment: The argument for not including a placebo group is accepted. With regard to the possibility of an active control, there are other treatments available and in use despite lack of regulatory approval, as summarised above, which could have been used for this purpose. However this would have involved a larger study and potential difficulties in interpretation particularly in the sense that there might be sub-populations more or less likely to respond to one treatment or the other. Furthermore the principal outcome variables are changes in laboratory measurements, for which a placebo response is unlikely to be observed. In summary, the study design is acceptable.

Study B2208/2208E1

This was a Phase II, proof of concept, open-label, uncontrolled study to assess the efficacy and safety of the short term (15 day) administration of pasireotide 600 µg BD to patients with Cushing's disease. The study, which has been published ⁽⁶⁾, was conducted at 10 international centres between April 2004 and June 2006, prior to the initiation of pivotal Study B2305, the design of which it presumably informed. It contains the only clinical data on the use of pasireotide in patients with Cushing's disease apart from the pivotal study, and is submitted in support of it.

Extension study B2208E1:

Patients who had either been classified as responders or "experienced significant clinical benefit" (which included having shown a reduction in mean urinary free cortisol (mUFC), but not to normal) in the core 15 day study were permitted to enrol in this six month Phase II extension, to continue on the 600 µg BD dose or have it increased to 900 µg BD if UFC levels rose during the extension. As in the original study, the primary efficacy variable was the proportion of responders based on normalisation of mUFC.

18 subjects, comprising three who had been responders in the core study, 11 who had shown a partial reduction of mUFC, and four who had shown no reduction, were evaluated in the extension study and remained on treatment from two months to 4.8 years with a

⁶ Boscaro M et al. 2009, Report of Study B2208: J Clin Endocrinol Metab. 94(1):115-22

mean duration of 16 months. At the time of data cut-off (March 2010), three patients were still receiving treatment.

The results were somewhat complex and are best summarised as follows:

- Of the three responders in the core study that entered the extension, one was still a responder at six months and one patient became a reducer. The third patient discontinued the study prior to Month 6 and was therefore counted as a non-reducer at six months.
- Of the 11 reducers in the core study that entered the extension, five maintained their reducer status at six months. Two of the reducers became responders at six months, and four became non-reducers.
- Of the four non-reducers in the core study that entered the extension, one became a responder at six months and three remained non-reducers.

Thus, there are similar numbers of responders after six months as at the end of the core study, but they are not the same subjects. Some subjects who responded well early experienced deterioration during the extension, and vice versa.

Comment: The status of the three patients who had been treated for almost five years is of interest if it can be presumed (latest data not seen) that they are showing a continuing response. The fact that they represent 10% of the original efficacy population is a significant clinical benefit.

Evaluator's overall conclusions on efficacy

A clinically valuable response occurred in approximately half of the patients treated in pivotal Study B2305, and in approximately half of those the urinary cortisol was returned to the normal range. Such a response was significantly more likely to occur if the higher dose of 900 µg BD was employed, by comparison with 600 µg BD. Biochemical evidence of response, when it occurs, is seen within the first month. Some form of reduction of urinary cortisol occurs in approximately two thirds of patients.

Although a higher response rate would obviously be preferred, these outcomes will be valued by clinicians caring for patients with Cushing's disease. Once the option of neurosurgical cure has been exhausted, as in the proposed indication, management becomes difficult and the efficacy outcomes described here are at least equivalent and probably superior to existing treatment options, in so far as the limited data on alternatives allows comparison. The inclusion of an active comparator arm, probably using ketoconazole, in the pivotal trial might have yielded a greater degree of confidence in the relative efficacy of pasireotide with respect to other treatments, but this was not undertaken. The logistics of such a trial would be complex.

The observation of pituitary tumour shrinkage in a significant proportion of patients is an additional treatment benefit.

Reliance on a single pivotal study appears acceptable in this case. The data comes from a wide international spread of specialised centres treating patients with this disorder, which mitigates against treatment or selection bias. Collection of a larger patient population would be difficult. Supporting Study B2208 and its extension contribute little in the way of patient numbers but qualitatively confirm the outcomes observed in B2305.

A significant concern is whether response rates will be maintained with long-term treatment, which would be required by the majority of patients receiving the product for the proposed indication.

If the application is approved, it is likely that the therapeutic benefits of pasireotide will be applied not only alone but in sequence or combination with other therapeutic agents, as

has already been described for its use in combination with cabergoline and ketoconazole in one study⁷ referred to in the Summary of Clinical Safety.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy study:

In the pivotal efficacy study, the following safety data were collected:

- AEs and serious adverse events (SAEs) were recorded and documented according to the study protocol at routine visits by means of historical data and monitoring of vital signs. AEs could be spontaneously volunteered or detected by questioning. The severity of AEs was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, as Grades 1-4 (mild, moderate, severe or life-threatening). Note that these same procedures and criteria for documentation of safety information were employed for all studies in the dossier.
- A number of AEs or safety issues of particular interest were defined for this study, as informed by the preclinical data, Phase I studies, and otherwise known adverse or potential adverse effects of somatostatin analogues. These included changes in blood glucose and related parameters, gallbladder related events, and effects on cardiac repolarisation.
- Laboratory tests, including haematology, blood chemistry and urine tests were performed at all protocol visits.
- Fasting blood glucose and HbA1c at regular intervals.
- ECG performed at all visits.
- Gallbladder ultrasound at baseline and every six months thereafter.

Study B2201/2201E

This study together with its long-term extension provides further safety data on acromegalic patients exposed to pasireotide at doses of 200, 400, and 600 µg BD. As the upper levels of these doses fall within the dose range proposed for the current application, or at least the lower part of it, the data is appropriately included in the safety database, and for the purposes of this evaluation.

Study B2202

This trial was carried out on patients with carcinoid syndrome. Doses given ranged from 300 - 900 µg BD. As shown below (Table 7), most patients were only treated short term (median exposure 12.7 weeks) but 15 received pasireotide for periods of between six and 12 months.

Study B2103

This study examined the efficacy and safety of pasireotide in patients with acromegaly. The primary objective was to compare the efficacy of single doses of 100 µg and 250 µg pasireotide with a standard 100 µg dose of octreotide (Sandostatin). The dosages of pasireotide used were employed early in the clinical development program and are not amongst the formulations submitted for market approval. A total of 12 patients received

⁷ Feelders RA, de Bruin C, Pereira AM, et al. 2010, Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. N Engl J Med; 362(19):1846-8

single doses as described above; this exposure does not contribute significantly to that of the safety population and is not included below in Table 7.

Summary of patient/drug exposure

Overall exposure to pasireotide in the studies reviewed for this submission is described below.

Table 7: Exposure to pasireotide and comparators in PK/PD studies.

Study ID	Controlled studies*			Uncontrolled studies	Total Pasireotide
	Pasireotide	Placebo	Moxifloxacin	Pasireotide	
B2101	54	18			54
B2102	28	28			28
B2106				17	17
B2107				66	66
B2108				43	43
B2112				4	4
B2113 part 1	37	18			37
B2113 part 2	95	95	95		95
B2125	112	112	112		112
C2101				78	78
B2114				34	34
B2216				45	45
B2124				90	90
TOTAL	326	271	207	377	703

*If a crossover study, subjects are counted in all relevant columns

Table 8: Exposure to pasireotide in clinical studies according to dose and duration.

Study ID (Indication)	Proposed dose range				Proposed maximum dose***			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n*	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n*
B2305 (Cushing's)	132	110	63	162	64	55	35	80
B2208 (Cushing's)				39				
B2208E1 (Cushing's)	17	12	7	19				
B2201 (acromegaly)**				62				
B2201E1 (acromegaly)	30	28	23	30				
B2202 (carcinoid)	22	15	7	45				
TOTAL	201	165	100	357	64	55	35	80

*The amount by which this figure exceeds the 3 month figure indicates patients treated for <3 months; if all columns to the left are blank, then all were treated for <3 months.

**Includes 400 µg BD and 600 µg BD dosage groups.

***A small number of patients included in the proposed dose range section of this table had doses of 1800 µg total daily for periods of their treatment but would not contribute significantly to the totals in this section.

Deaths and other serious adverse events

Pivotal study:

Amongst the recruited patients, two deaths occurred, one during the screening period prior to any administration of study drug and the other two months following study completion, due to surgical complications following adrenalectomy.

Comment: Neither of these deaths is related to study drug, but the second is a vivid illustration of the difficulties which management of pituitary Cushing's disease can present. The patient was aged 47, had failed pituitary surgery, started pasireotide but then developed worsening diabetes so was discontinued from the study and was referred for adrenal surgery with an eventually fatal outcome. The clinical evaluator mentioned this case because it illustrates the level of need for an effective medical treatment, and therefore the level of risk which might be tolerable in achieving such.

SAEs were reported overall in 24.7% of patients, with no significant differential between the dosage groups. The pattern of events was similar to that for AEs generally with the addition of some instances of "pituitary dependent Cushing's syndrome" and "pituitary tumour benign", clearly related to the underlying disease. Otherwise the most common events are related to blood glucose or gallstone disease. There is no suggestion of any safety issues other than those already recognised.

Other studies:

The only death reported in the remainder of the safety database was that of a single patient in the carcinoid dataset, related to tumour progression.

SAEs in the remaining studies were reported in 20-30% of the study populations and most commonly consisted of hyperglycaemia related events, or other AEs of known special interest related to the study medication, or incidental disorders such as acute myocardial infarction or pregnancy.

Evaluator's overall conclusions on clinical safety

Pasireotide, similar to other somatostatin analogues, has a significant profile of observed and potential adverse effects. Upper GI symptoms and diarrhoea will be observed in about half of the patients treated with therapeutic doses, although usually improving with time. The high incidence of these adverse effects reflects the fact that the doses required for adequate therapeutic response are close to the maximum tolerated dose. Gallstones will develop in up to 20% of patients.

Hyperglycaemia of some degree develops in most Cushing's disease patients treated with pasireotide, and will meet the criteria for diabetes mellitus in about half of these. If this does develop, it responds best to those oral agents which act through the incretin mechanism, or could otherwise be treated with insulin.

A minor degree of QT prolongation has been observed but has not been the cause of serious cardiac clinical events.

Abnormalities of liver function have developed with initiation of pasireotide, but have usually been mild and transient. However, there is insufficient evidence of safe use in patients with moderately impaired hepatic function, even at the reduced dosage proposed by the sponsor.

First round benefit-risk assessment

Patients with pituitary Cushing's disease who have failed or are otherwise unsuitable for curative pituitary surgery are faced with two equally undesirable alternatives. Therefore, if a treatment offers significant benefits it might justify the taking of significant risks.

First round assessment of benefits

The benefits of pasireotide in the proposed usage are:

- Reduction of urinary cortisol secretion and consequent improvement in clinical and biochemical manifestations of Cushing's disease.
- Potential avoidance of long-term complications of cortical exposure provided a response is maintained.
- Reduction in pituitary tumour volume.

Although no other medical therapies are currently approved for Cushing's disease, the benefits demonstrated in this application are, on the basis of limited evidence available, equivalent or superior to current off-label use of other medications, as discussed above.

First round assessment of risks

The risks of pasireotide in the proposed usage are:

- Development of GI adverse effects such as diarrhoea and nausea. These are unpleasant but not permanently injurious to health.
- Development of hyperglycaemia with a significant chance of progression to diabetes mellitus requiring treatment, possibly insulin injections.
- Approximately 20% risk of developing gallstones, but little risk of bile duct obstruction.
- Development of QT prolongation, although with little likelihood of any risk of cardiac compromise except in the case of significant pre-existing comorbidity or co-administration of medications with a similar effect.
- Mild impairment of liver function (raised enzyme levels); the possible impact of this, along with other exposure-related effects of pasireotide, on patients with moderately impaired hepatic function has not been adequately assessed and therefore represents an unquantifiable risk in relation to likely benefit for that subpopulation.

First round assessment of benefit-risk balance

The benefit-risk balance of pasireotide, given the proposed usage, is favourable with the exception that, in the evaluator's view, use by patients with moderately impaired hepatic function should not be recommended even at reduced dosage without further evidence that this is safe. This recommendation is based on the evaluator's assessment that the benefit-risk balance appears, in the absence of definitive data, to be significantly less favourable than for the overall Cushing's disease population.

First round recommendation regarding authorisation

It is recommended that the application be approved; pending consideration of the recommendations of this report regarding safety of use in the presence of moderately impaired hepatic function. It is also suggested that the proposed indication be altered to:

Treatment of patients with Cushing's disease for whom pituitary surgery is contraindicated or has failed

as this defines the target population more precisely and is more consistent with the population studied in the pivotal clinical trial.

List of questions

None requested.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan identified as Safety Risk Management Plan (in EU-RMP format) Version 2 (dated 13/01/2012, DLP 17/11/2011) with Safety Risk Management Plan Australian Implementation Version 2 (dated 21/09/2012) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 9):

Table 9: Important identified and potential risks and missing information.

Category	Safety concern
Important identified risks	Hypocortisolism/Cortisol withdrawal syndrome Hyperglycemia Bradycardia QTc interval prolongation Cholelithiasis Hematological abnormalities Liver enzymes increased Injection site reactions Gastrointestinal disorders
Important potential risks	Clinically significant GH/IGF-I decrease Hypothyroidism
	Pancreatitis Coagulation abnormalities Hypotension Hypocalcemia Gastrointestinal erosions/bleedings Potential interactions with cyclosporine, drugs metabolized by CYP3A4, bromocriptine, antiarrhythmic medicines and antidiabetics Off-label use in children and other indications Allergic reactions/immunogenicity Tumor expansion
Important missing information	Pregnancy and Breast-feeding Elderly patients Patients with cardiac diseases (such as unstable angina, congestive heart failure, recent myocardial infarction or clinically significant bradycardia) Children and adolescents (patients < 18 years) Patients with liver diseases Long-term safety in patients

Office of Product Review (OPR) reviewer comment:

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS this is considered acceptable.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 10.

Table 10: Activities additional to routine planned by the sponsor regarding certain safety concerns

Additional activity	Assigned safety concern	Actions/outcome proposed
CSOM230B2410 Non-interventional study for the generation of long term safety and efficacy data of pasireotide sc in patients with Cushing's disease Protocol available	Long-term safety in patients	Primary objective: To document the long-term safety and tolerability profile of pasireotide sc when administered as monotherapy or in combination with other therapies in patients with Cushing's disease. Secondary objectives: Multiple (See study protocol)

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones:

The sponsor mainly plans routine pharmacovigilance activities. Only one safety concern has been assigned an additional activity.

The sponsor's proposed pharmacovigilance activities and milestones are considered acceptable, but not complete. The study protocol submitted is considered acceptable in regard to the assigned safety concern for RMP purposes.

Given the risk of pasireotide-induced hyperglycaemia and the profile of the likely target population, the sponsor should conduct a post-marketing clinical study to assess the management of this safety concern. In particular, this should establish which anti-diabetic drug class to use, as biguanides (for example, metformin) or thiazolidinediones (for example rosiglitazone) may be less favourable than others, such as DPP-4 inhibitors or GLP-1 analogues (van Raalte et al., 2011⁸). It is noted that the sponsor plans to undertake such a study in a different jurisdiction.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor states that no additional risk minimisation activities are necessary.

OPR reviewer comment:

The sponsor's conclusion is acceptable, except for the potential need of patient education on the safe techniques in regard to administering pasireotide safely and effectively.

⁸ van Raalte DH, van Genugten RE, Linszen MML, Ouwens DM, Diamant M, 2011. Glucagon Like Peptide-1 Receptor Agonist Treatment Prevents Glucocorticoid-Induced Glucose Intolerance and Islet-Cell Dysfunction in Humans. *Diabetes Care* 34(2): 412-417.

Potential for medication errors

For the purposes of this RMP evaluation different types of medication errors, as suggested by Ferner & Aronson (2006)⁹, have been considered.

OPR reviewer comment:

The sponsor's actions regarding name confusion, labelling and presentation are considered acceptable. However, medication errors may arise from improper administration of the drug

The sponsor should outline their proposed activities (including potential additional risk minimisation activities) that ensure that patients are able to retrieve the drug from the ampoule safely and effectively, inject the drug safely and effectively, and dispose of the sharp safely and effectively.

Potential issues may include and are not limited to:

- Injury sustained from the glass ampoule;
- Dosing variation resulting from the inability to draw up the correct amount contained in the ampoule;
- An incorrect injection technique that results in sub dermal or intramuscular injections; and
- Failure to dispose of the sharp appropriately and risk of transmission of disease to others.

Potential for overdose

The risk for overdose is low. In the proposed PI, over-dosage and its management have been discussed to a satisfactory standard.

Potential for off-label use

Somatostatin analogs such as pasireotide could potentially be used to manage acromegaly and carcinoid tumours.

Potential for paediatric off-label use

The sponsor recognises that pasireotide is only indicated for adults. This is reflected in the proposed PI. This is considered acceptable.

Risk minimisation plan**Planned actions**

No additional risk minimisation activities are proposed for Signifor.

OPR reviewer comment:

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised.

⁹ Ferner RE, Aronson JK, 2006. Clarification of terminology in medication errors: definitions and classification. Drug Saf 29:1011-1022.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP (Safety Risk Management Plan (in EU-RMP format) Version 2 (dated 13/01/2012, DLP 17/11/2011) with Safety Risk Management Plan Australian Implementation Version 2 (dated 21/09/2012)) is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft product information and Consumer Medicine Information documents should NOT be revised until the Delegates Overview has been received.

Further safety considerations

- Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for further information. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered:

Recommendations in regard to pharmacovigilance activities

Given the risk of pasireotide-induced hyperglycaemia and the profile of the likely target population, the sponsor should conduct a post-marketing clinical study to assess the management of this safety concern.

Recommendations in regard to risk minimisation activities

The sponsor should outline their proposed activities (including potential additional risk minimisation activities) that ensure that patients are able to retrieve the drug from the ampoule safely and effectively, inject the drug safely and effectively, and dispose of the sharp safely and effectively.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised.

Suggested wording for conditions of registration

Implement Safety Risk Management Plan (in EU-RMP format) Version 2 (dated 13/01/2012, DLP 17/11/2011) with Safety Risk Management Plan Australian Implementation Version 2 (dated 21/09/2012), and any future updates as a condition of registration.

Reconciliation of issues outlined in the RMP report

Table 11: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for further information.		

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
<p>It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.</p>		
<p>Given the risk of pasireotide induced hyperglycaemia and the profile of the likely target population, the sponsor should conduct a post-marketing clinical study to assess the management of this safety concern.</p>	<p>The sponsor will be conducting 'Study SOM230B2219 is "A 24 week multicenter, open-label, Phase IIIb study to investigate the management of pasireotide-induced hyperglycemia in adult patients with Cushing's Disease and acromegaly with insulin- or DPP-4 inhibitor targeted therapy".'</p> <p>The purpose 'is to investigate the optimal management of pasireotide-induced hyperglycemia in patients with Cushing's Disease or acromegaly in the overall population. The study aims to demonstrate that hyperglycemia can be effectively and safely managed in the majority of patients, including those with diabetes at baseline who are not at goal (HbA1c > 7%) as evidenced by lower or stable HbA1C or only a small increase from baseline in HbA1c at week 16 (i.e., ≤0.3%). This study is also designed to provide guidance on the optimal treatment algorithm with specific focus on DPP-4 inhibitor therapy, i.e., sitagliptin (first DPP-4 inhibitor approved, available in US and EU) vs. insulin.'</p>	<p>This is considered acceptable. The study and the study protocol needs to be included in any RMP updates.</p>
<p>The sponsor should outline their proposed activities (including potential additional risk minimisation activities) that ensure that patients are able to retrieve the drug from the ampoule safely and effectively, inject the drug safely and effectively, and dispose of the sharp safely and effectively.</p> <p>Potential issue: Injury sustained from the glass ampoule.</p>	<p>The sponsor acknowledges that glass ampoules are not an ideal delivery system. The sponsor states that the following encompasses adequate risk minimisation measures:</p> <ul style="list-style-type: none"> • Use of OPC (one point cut) ampoules; • Use of Schott TopLine ampoules; and • Amendment of the proposed CMI to reflect recommendations made in the RMP evaluation report. <p>The sponsor has suggested appropriate changes to the proposed</p>	<p>This is considered acceptable</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	CMI including the use of illustrations. These changes have been outlined in the s31 response document.	
Potential issue: Dosing variation resulting from the inability to draw up the correct amount contained in the ampoule.	The sponsor has suggested appropriate changes to the proposed CMI including the use of illustrations. These changes were outlined in the TGA request for further information document.	This is considered acceptable.
Potential issue: An incorrect injection technique that results in sub-dermal or intramuscular injections.	The sponsor has suggested appropriate changes to the proposed CMI including the use of illustrations. These changes were outlined in the TGA request for further information document.	This is considered acceptable.
Potential issue: Failure to dispose of the sharp appropriately and risk of transmission of disease to others.	The sponsor has suggested appropriate changes to the proposed CMI including the use of illustrations. These changes were outlined in the TGA request for further information document.	This is considered acceptable.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The pharmaceutical chemistry evaluator has no objection to registration.

In HV, T_{max} is 0.25-0.50 hours. Pasireotide shows linear pharmacokinetics in both HV and Cushing's disease patients over the dose range studied, which includes the proposed therapeutic doses. The effective $t_{1/2}$ is approximately 12 hours. In plasma, it is 88% protein bound.

No studies have been conducted to evaluate the absolute bioavailability in humans. Pasireotide is metabolically stable and is mainly eliminated via hepatic clearance (biliary excretion) and only to a small extent via renal route. Relative to patients with intact hepatic function, patients with mild, moderate and severe hepatic impairment (Child-Pugh A, B, C) show an 8%, 60%, 79% increase in AUC_{inf} , and a 7%, 67%, 69% increase in C_{max} (Study B2114) after adjustment for age, BMI and albumin. Based on these data, the proposed PI recommends dose adjustment in patients with moderate hepatic impairment and contraindication of pasireotide use in patients with severe hepatic impairment. The clinical evaluator had some concerns with this.

Based on in vitro studies, pasireotide is not a substrate, inhibitor, or inducer for metabolic isozymes in the proposed dosing range, and therefore unlikely to be subject to drug-drug interactions.

Pasireotide was evaluated for potential QT prolongation in two QT studies. Testing was conducted with one of the therapeutic doses (600 µg) and with a suprathreshold dose of 1950 µg to simulate a possible "worst case scenario" such as administration to patients

with hepatic impairment. In both studies an effect of pasireotide on the QTc interval was observed. The maximum placebo-subtracted mean change from baseline occurred at two hours post dose. Pasireotide increased the double-corrected QTc interval by 13.19 ms (90% confidence interval (CI): 11.38; 15.01) and 16.12 ms (90% CI: 14.30; 17.95 ms) following 600 µg BD and 1950 µg BD, respectively. The PI will need to clearly and explicitly convey this information.

Nonclinical evaluation

There were no unexpected findings identified with pasireotide and the toxicity profile is consistent with other somatostatin analogues.

The toxicities observed in toxicology studies are described as extensions of the pharmacologic activity of the drug and are consistent across species. Pasireotide was not found to be genotoxic. Carcinogenicity studies were negative for drug-related neoplasms.

With respect to hyperglycemia and hepatic AE (two safety concerns identified in humans during the pasireotide program), the animal data provide only limited insight. The observation that pasireotide inhibits insulin secretion was made in animals and in humans. Overt hepatic toxicity was not observed in healthy animals.

Because reproduction studies performed in rats and rabbits showed evidence of impaired fertility or harm to the fetus at therapeutic pasireotide exposures, a pregnancy C category is recommended, indicating that pasireotide should be used during pregnancy only if clearly needed. Patients with Cushing's disease, in general, have low fertility rates because of the effects of cortisol on the reproductive system; and, for patients who undergo pituitary surgery, because of a higher likelihood of pituitary insufficiency.

Pasireotide also had an inhibitory effect on GH/IGF-1 secretion in animals, which is the basis for it being developed for the treatment of acromegaly.

Clinical

The clinical evaluator recommended that the application be approved, although he/she raised two areas of uncertainty concerning the PI:

- Use in patients with moderate hepatic impairment.

The dosage recommendations in the initially proposed PI were:

- No dose adjustment for mildly impaired hepatic function (Child-Pugh A)
- An initial dose of 300µg twice a day for moderately impaired hepatic function (Child-Pugh B). The maximum recommended dose is 600 µg twice a day.
- Contraindicated for patients with severe hepatic impairment (Child Pugh C).

In response to the evaluator's concern about use in moderate hepatic impairment, the sponsor added the following extra information about the initial dose of 300µg and possible titration to 600µg (2nd point above): "only following careful consideration of perceived risks and benefits to the individual and with frequent clinical review and monitoring of liver function".

- The wording of the indication: The clinical evaluator preferred *Treatment of patients with Cushing's disease for whom pituitary surgery is contraindicated or has failed* because "this defines the target population more precisely and is more consistent with the population studied in the clinical trial". The sponsor made this change during the evaluation.

The data evaluated included:

- 12 clinical pharmacology studies, including 11 that provided PK data and nine that provided PD data.
- One pivotal efficacy/safety Study B2305
- Four other efficacy/safety studies.
- Population safety reports on glucose metabolism, QT/QTc (cardiac safety), and a hepatic safety report

The main evidence of efficacy of pasireotide in patients with Cushing's disease comes from Phase III Trial B2305. Supporting evidence comes from the Phase II Trial B2208.

Pharmacology

Following subcutaneous injection, pasireotide was shown to have:

- Rapid absorption
- Dose proportionality across the proposed therapeutic doses
- No significant interference by metabolites
- Major dependence on hepatic excretion

Pharmacodynamics

Pasireotide has several secondary PD actions which reflect widespread inhibitory role of SST. Two are particularly noteworthy:

- Physiological GH secretion is suppressed at a lower dose threshold than the therapeutic dose used in Cushing's disease.
- Maximal effects on glucose homeostasis occurs at any dose within the therapeutic range for Cushing's disease; so downward adjustment of dose is unlikely to ameliorate hyperglycaemia/diabetes.

Efficacy

The pivotal evidence of efficacy for pasireotide in patients with Cushing's disease comes from the Phase III Clinical Trial B2305, which is the largest Phase III study conducted in Cushing's disease patients, for any therapy. Supportive evidence comes from the Phase II Clinical Trial B2208.

Table 12: Study B2208 (Phase II, supportive)

Patients	39 adult patients with Cushing's disease
Intervention	600 µg pasireotide BD, administered subcutaneously
Comparator	nil
Primary endpoint	urinary free cortisol (UFC)
Follow-up	15 days (patients were allowed to participate in an extension phase at which time up- or down- titration of the pasireotide dose was allowed)

Results: 5/29 (17%) of the patients who contributed data showed normalisation of UFC.

Comment: This study showed that 600 µg of pasireotide BD can normalise UFC in some patients. Dose response analysis showed that patients who normalised had higher exposures to pasireotide than non-responders and this led to exploration of 900 µg BD in the extension phase of this trial and the addition of a 900 µg arm to the planned Phase III Trial B2305.

Table 13: Study B2305 (Phase III, pivotal evidence provided to establish efficacy)

Patients	162 adult (18+ years) patients with Cushing's disease enrolled at 68 sites in 18 countries. The trial only enrolled Cushing's disease patients who were candidates for medical therapy according to current practice: patients with persistence or recurrence of hypercortisolism despite prior pituitary surgery (that is, second 2nd line), plus some patients who refused surgery or were poor candidates for surgery (78% were women). The study had clear inclusion criteria to confirm Cushing's disease and exclude non-Cushing's patients. 4% of patients had prior radiotherapy.
Intervention	600 µg versus 900 µg pasireotide BD, administered subcutaneously
Comparator	nil (only rarely does Cushing's disease resolve/improve spontaneously)
Design	<p>Parallel randomised controlled trial.</p> <p>A potential carry-over effect of previous medications was minimised by a washout of previous medical therapies that took into account the half-life of specific drugs.</p> <p>The study protocol did not allow patients to continue pasireotide treatment at the randomised dose if they failed to show improvement. By three months of treatment, patients who did not reach a UFC level that was clearly trending towards normalisation were unblinded and allowed to increase their dose by 300µg. Patients for whom the dose could not be escalated were discontinued from the trial. All patients, who were unblinded at three months, were considered treatment failures in for the purpose of the primary endpoint. (Only 66% of patients completed the first six months of the trial due to a combination of poor response and adverse events.)</p>
Primary endpoint	<p>Normalised EFC (at or below the ULN range at six months without a dose increase).</p> <p>UFC was measured as an average of multiple urine collections and is referred to as the mUFC for each time point for each patient.</p>
Follow-up	Six months for primary outcome (double blinding), with a six months extension (open label); and further follow-up after 12 months.

Pre-planned analysis: The two different doses were not compared to each other. Instead, each dose was independently compared to a threshold, set by FDA, of a 15% response rate. (Spontaneous remission of Cushing's disease is an exceedingly rare event.)

Sample size/power: 73 patients in each group would provide 87% power to demonstrate statistical significance at 5% against the 15% threshold.

Table 14: Primary efficacy endpoint at 6 months

	Pasireotide 600 µg BD, n=82	Pasireotide 900 µg BD, n=80	Total N=162
Normalisation of UFC; n/N (%)	12/82 (15%)	21/80 (26%)	33/162 (20%)
95% CI	7%, 22%	17%, 36%	14%, 27%
97.5% CI		16%, 39%	

The lower limit of the 95% CI was above the pre-specified threshold of 15% for the 900 µg dose, but not the 600 µg dose. The 900 µg dose also achieved the threshold of 15% using a 97.5% CI, to allow for multiplicity.

Results: Secondary endpoints and post-hoc analyses

Partial response was defined as six month mUFC remaining above the upper limit of normal (ULN), but decreasing by at least 50% from baseline. 600µg: 15/82 or 18%, 900 µg: 10/80 or 12.5%; total 25/162 or 15%.

Mean mUFC levels decreased by 52% (600 µg) and 58% (900 µg). Serum ACTH and cortisol levels decreased, but none normalised. There were decreases other efficacy endpoints (for example, BP, weight, and health-related quality of life) but these are difficult to interpret because: there was no placebo group; other medications were at the discretion of the treating doctor; there was no adjustment for statistical multiplicity.

Seventy five patients (46%) had a measurable pituitary tumour on MRI at baseline. At Month 12, the mean percentage change in tumour volume was -9.1% (95% CI, -46.3 to 28.0) in the 600 µg group and -43.8% (95% CI, -68.4 to -19.2) in the 900 µg group.

Efficacy and dose selection

The 900 µg dose achieved statistical significance against the 15% threshold; whereas the 600 µg dose did not. However, the difference for some of the secondary endpoints was small; and the 600 µg was not directly compared to the 900 µg dose. Also, the pre-specified threshold of the responder (normalisation of UFC) percentage of 15% was somewhat arbitrary and was adopted because of the need to pre-specify the analysis plan and have a formal statistical argument for sample size. Furthermore, because of tolerability, some patients in the 600 µg group finished the trial on 300 µg and some patients on 900 µg finished the trial on 600 µg.

Taking into consideration the totality of the efficacy analyses, the 900 µg BD dose seems to perform somewhat better than the 600 µg BD dose (a larger percentage of patients normalised their mUFC or had mUFC reductions > 50%), but the differences were not striking. The two doses may not be very far away on the dose-response curve.

Safety

Currently available data

The safety data provided included information obtained from the Phase II trial and the Phase III trial (including extensions to 12 months and beyond), from several studies conducted in HV, and from studies across all indications for which pasireotide is being developed (including acromegaly).

The safety datasets included 726 people, 201 of whom were patients with Cushing's disease; 162 were enrolled in the pivotal Phase III Trial B2305 where mean exposure was close to 11 months and 40% of patients were treated for 12+ months.

Overview of adverse events

No patient deaths were reported while on pasireotide treatment. *SAES* occurred in about one-quarter of the patients in the pivotal Phase III Trial B2305. Even in the absence of a comparator arm in the trial, some *SAEs* are likely to be pasireotide-related, based either on known mechanism of action (for example, adrenal insufficiency) or based on the already characterised pattern of *SAEs* observed with other somastatin inhibitors: GI *AEs* (abdominal pain, constipation, increased lipase food intolerance), hepatobiliary disease (cholelithiasis, acute cholecystitis), QT prolongation, hyperglycaemia, diabetes, hypoglycaemia. Trial discontinuations for *AEs* occurred in 17.3% of patients, with a similar pattern to that observed for *SAEs*.

Given the morbidity seen in patients in Cushing's disease, treatment-emergent *AEs* were seen in almost all patients (98%). The most frequent were: diarrhoea (58%), nausea (52%), hyperglycaemia (40%), cholethiasis (30%), headache (28%), abdominal pain (24%), and diabetes (18%).

In the Phase III Trial B2305, QT prolongation was reported in 6% of patients; no events of torsade de pointes were diagnosed (as described in the section on Pharmaceutical Chemistry, QT prolongation was confirmed in two QT trials). Hypocortisolism was seen in 8.0% trial participants, but only about one quarter required exogenous steroid treatment and only for a short duration.

Adverse events of particular concern

1. Hyperglycaemia and diabetes

Pasireotide treatment is associated with a remarkable degree of hyperglycaemia, an issue of particular concern given that patients with Cushing's disease already have insulin resistance due to their hypercortisolism. In pivotal Phase III Trial B2305, increases in fasting plasma glucose occurred as early as two weeks after start of treatment; a mean increase in HbA1c from baseline of 1.5% was seen in both dose groups. The percentage of patients with diabetes increased from 34% at baseline to 50% at all subsequent time periods. A new anti-diabetic medication was started in 74 of the 162 participants in Trial B2305.

The mechanism of pasireotide-induced hyperglycaemia is well characterised and is consistent with the somatostatin receptor binding profile of pasireotide. Somatostatin-related inhibition of insulin secretion is almost entirely mediated by the sstr2 and sstr5, and pasireotide and pasireotide has high affinity for both these receptors, in contrast with the binding profile of the other currently marketed somstatin receptors, lanreotide and octreotide, which have lower sstr5 affinities and have shown lower glucose elevation in clinical trials.

2. Liver function

Liver enzyme elevations have been seen previously with somatostatin analogues. In B2305, 5.1% of patients had elevations of ALT and AST three times the ULN. The general experience with octreotide and lanreotide is that these liver enzyme elevations are mostly benign, transient, and reversible.

Safety and dose selection

The safety profiles of the two different doses, evaluated in the pivotal Trial B2305, were not very different. Discontinuations were only slightly higher in the 900 µg group: 18.8% versus 15.9%; as were *AEs* related to glucose metabolism: 42.5% versus 37.8%: DM: 20%

versus 15.9%. A possible explanation is that trough levels were not very different between the two doses.

Risk Management Plan

Implement EU RMP, Version 8.0 (dated Oct 2012) with Australian Specific Annex to the EU RMP Version 8.0, Version 1.0 (dated Nov 2012).

Delegate considerations

Although the pivotal Phase III Trial B2305 did not have a placebo arm, Cushing's disease only rarely resolves spontaneously. Therefore, the Phase III Trial is adequately designed to establish efficacy. The endpoint in the trial, UFC is an established biomarker for diagnosing and monitoring response to treatment in Cushing's disease. Effects of pasireotide on patient-relevant outcomes such as cardiovascular events, depression, and muscle weakness are unknown. However, it would be unrealistic to expect that a large enough trial, with long enough follow-up, could be conducted for such a rare condition.

The pivotal Phase III Trial B2305 is the largest randomised study of a treatment for Cushing's disease. Therefore, the risks/safety profile of pasireotide is probably better characterised than other medicines for Cushing's disease, which are used off-label. The Delegate had no reason to say, at the time, that the application for pasireotide should not be approved for registration.

Proposed action

Specific questions for ACPM advice are:

1. **Starting Dose:** The proposed Australian PI recommends a starting dose of 900 µg, with titration back to 600 µg based on response and tolerability. Only the 900 µg dose was statistically significant versus the pre-specified threshold of at least 15% of patients achieving normalisation of their UFC at six months. However, differences on efficacy endpoints, compared to the 600 µg dose, were not striking; differences on safety endpoints were also not striking. Would it be better to recommend a starting dose of 600 µg with possible up-titration to 900 µg? (As in EU, see Table 1). Alternatively, should the PI just recommend a dose range of 300 µg-900 µg? (As in US, see Table 1).
2. **Dose adjustments for hepatic impaired patients:** Pasireotide is eliminated via hepatic excretion. Relative to patients with intact hepatic function, patients with mild, moderate, and severe hepatic impairment (Child-Pugh A, B, C) show a 12%, 56%, 42% increase in AUC_{inf} , and a 3%, 46%, 33% increase in C_{max} (Study B2114). Based on these data, the proposed PI recommends dose adjustment in patients with moderate hepatic impairment and contraindication of pasireotide use in patients with severe hepatic impairment. Do the data (or expert clinical opinion) support such a recommendation? Is the general advice about liver monitoring for patients without hepatic impairment adequate? (Prior to treatment; after one to two weeks, after two to three months; and then as clinically indicated)
3. In the context of the seriousness of Cushing's disease, are the adverse effects manageable? In particular, can hyperglycaemia (which is seen almost immediately with increases in fasting plasma glucose noted within two weeks) be managed?

The sponsor could address the following questions in the pre-ACPM response:

- What post-marketing studies planned to assess the management of pasireotide induced hyperglycaemia and diabetes?
- Are any registry/database studies planned to describe patterns of use of pasireotide and outcomes of use?

Conditions of registration:

The following are proposed as conditions of registration:

- Implement Safety Risk Management Plan (in EU-RMP format) Version 2 (dated 13/01/2012, DLP 17/11/2011) with Safety Risk Management Plan Australian Implementation Version 2 (dated 21/09/2012), and any future updates.
- Provide to the TGA the results of any studies that identify safety concerns or provide updated safety information, as soon as possible.
- Provide to the TGA the results of any studies that assess the management of pasireotide-induced hyperglycaemia or diabetes, as soon as possible.

Response from Sponsor

Introduction

Novartis welcomes the Delegate's and clinical evaluator's recommendation to approve Signifor (pasireotide) for:

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

Pasireotide is a new chemical entity in Australia and for this submission and indication, pasireotide is an orphan drug. Cushing's disease is a very rare debilitating and life-threatening endocrine disease for which there is no registered treatment in Australia. The Delegate has sought the ACPM's advice on three specific issues related to this application and has also invited Novartis to respond to two questions relating to planned post marketing studies. Novartis will take this opportunity to present our responses on each of these specific issues for consideration by ACPM. For the sake of clarity and convenience, the Delegate's comments are transcribed in italics ahead of our response.

Response to issues raised in the Delegate's overview

Question 1: Starting dose

The proposed Australian PI recommends a starting dose of 900 µg, with titration back to 600 µg based on response and tolerability. Only the 900 µg was statistically significant versus the pre-specified threshold of at least 15% of patients achieving normalisation of the UFC at six months. However the differences on efficacy endpoints, compared to the 600 µg dose were not striking; differences on safety endpoints were also not striking. Would it be better to recommend a starting dose of 600 µg with possible up-titration to 900 µg? (As in the EU, see Table 1). Alternatively, should the PI just recommend a dose range of 300 µg – 900 µg? (As in the US, see Table 1).

Response

The biological (biochemical) efficacy assessment of 600 µg and 900 µg BD indicates that both doses are efficacious. The key parameter of median changes in mUFC over time showed similar results between the two doses with median changes from baseline to Month 6 being identical at -47.9% and the Month 12 values being very close at -67.6% and

-62.4%, respectively for 600 µg and 900 µg BD [Pivotal clinical Study B2305 CSR]. Changes in the other biological parameters of plasma ACTH and serum cortisol for the two dose groups were also similar. In addition, the clinical changes observed did not appear to be dose dependent, nor was there a difference in the persistence of effect between doses. However, controlled and partially controlled responder rates were slightly higher for 900 µg BD (41.3%) relative to 600 µg BD (34.2%) with a larger percentage of patients on 900 µg BD meeting the primary endpoint and demonstrating a more consistent effect across all baseline mUFC values [Summary of Clinical Efficacy].

As presented in the B2305 CSR as well as the Summary of Clinical Safety, key safety parameters (for example, QT prolongation, elevations in liver function tests, and cardiovascular events) lacked any dose-dependency with the possible exception of hyperglycaemia. Normal glucose tolerance patients and pre-diabetic patients did not appear to have meaningful differences in HbA1c between 600 and 900 µg BD. Diabetic patients on 900 µg BD had a tendency for slightly larger increases in HbA1c relative to 600 µg BD. Hyperglycaemic AEs were assessed by dose and baseline glycemic status using the Adverse Events of Special Interest-hyperglycaemia search terms previously used in the B2305 CSR and the Summary of Clinical Safety. Overall, the analysis did not reveal clear differences between 600 and 900 µg BD across the groups studied (normal glucose tolerance, pre-diabetics and diabetics). The similarity between 600 and 900 µg BD in mean changes in HbA1c over time is consistent with the mechanistic data observed in Study B2216. One of the main conclusions of Study B2216 was that there were no dose dependent differences in any of the key outcome measures (that is, oral glucose tolerance test (OGTT), hyperglycaemic clamp and the hyperinsulinemic euglycaemic clamp).

The effect of up-titration of pasireotide was reviewed in an analysis presented in the clinical study report for study B2305. There were 24 patients in the 600 µg BD group whose dose was increased at Month 3. In those patients whose dose was increased from 600 to 900 µg BD at Month 3, the mean mUFC decreased from 710.4 nmol/24h at Month 3 (before dose increase) to 571.3 nmol/24h at Month 4 (after dose increase). The median mUFC decreased from 530.8 to 402.0 nmol/24h for the same time points.

Based on the greater efficacy and consistency of effect observed with the 900 µg BD dose when compared with the 600 µg BD dose of pasireotide, Novartis recommends a starting dose of 900 µg BD except for patients with a history of diabetes or pre-diabetes, in whom the recommended starting dose is 600 µg BD and patients with moderately impaired hepatic function in whom the recommended starting dose is 300 µg BD. Thus the relevant text in the PI has not been altered pending further advice from the ACPM.

Question 2: Dose adjustments for hepatic impaired patients:

Pasireotide is eliminated via hepatic excretion. Relative to patients with intact hepatic function, patients with mild, moderate, and severe hepatic impairment (Child-Pugh A, B, C) show a 12%, 56%, 42% increase in AUC_{inf} and a 3%, 46%, 33% increase in C_{max} (Study B2114). Based on these data, the proposed PI recommends dose adjustment in patients with moderate hepatic impairment and contraindication of pasireotide use in patients with severe hepatic impairment. Do the data (or expert clinical opinion) support such a recommendation? Is the general advice about liver monitoring for patients without hepatic impairment adequate? (Prior to treatment; after one to two weeks, after two to three months; and then as clinically indicated).

Response

Novartis has arrived at the proposed recommendations for dosing in hepatic impaired patients based on the evidence provided by the PK data. In hepatic impairment Study B2114, results showed after adjustment for age, BMI and albumin, subjects with mild, moderate and severe hepatic impairment based on Child-Pugh classification had 8%, 60% and 79% increase in AUC_{inf} , and 7%, 67% and 69% increase in C_{max} in comparison to the

normal group. Study B2114 employed a single sc dose of 600 µg. Based on the assumption of dose proportionality, a reduction of dose from 600 µg to 375 µg BD, would result in a 60% decrease in AUC_{inf}. Similarly, a reduction of dose from 600 µg to 359 µg BD, would result in a decrease in C_{max} by 67% for moderate hepatic impaired patients. Practically, the closest dose strength to 375 µg BD and respectively 359 µg BD is 300 µg BD. Thus the recommendation is that the maximum dose for patients with Cushing's disease with moderate hepatic impairment is 600 µg BD with a starting dose of 300 µg BD.

Pasireotide use in patients with severe hepatic impairment is not recommended, given that PK exposures in patients with Cushing's disease are two-fold higher than those in HV, and 69% to 79% higher PK exposures in subjects with severe hepatic impairment than with normal hepatic function. Elevations of liver enzymes and total bilirubin have been observed throughout the clinical study program. Increases in liver function test measures were observed for 16% of patients with Cushing's disease in the pivotal Study B2305; however these increases were generally mild. Patients with severe hepatic impairment may be intrinsically more sensitive to liver enzyme and bilirubin elevations seen as side effects of pasireotide sc. As a precautionary measure, patients with Cushing's disease and severe hepatic impairment should not be treated with pasireotide sc.

The proposed PI provides recommendations for liver monitoring in patients. Novartis would like to add that at the time of submission of the response the TGA's request for further information, a safety update (CDS 31-Jan-13) to the Precautions, Liver tests section to the Australian PI was included. To provide further guidance to treating physicians on the monitoring of liver function, an additional time point up to three months was proposed. Mild and transient elevations of liver tests in both Cushing's disease patients and healthy subjects were observed mostly during the first three months of treatment. Accordingly, Novartis proposed to increase liver monitoring during this period. Therefore the monitoring proposal is "Monitoring of liver function is recommended prior to treatment with Signifor and after the first one to two weeks and then monthly for three months. Thereafter liver function should be monitored as clinically indicated."

Adverse Effects: particularly hyperglycaemia

Management of AEs: in the context of the seriousness of Cushing's disease, are the adverse effects manageable? In particular, can hyperglycaemia (which is seen almost immediately with increases in fasting plasma glucose noted within two weeks) be managed?

Response

In patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed control of hypercortisolism, may currently be attempted with off-label use of various medications, such as ketoconazole. Although this is used in Australia, it can be toxic at the doses required to reduce cortisol secretion. Both the FDA and EMA have made recent recommendations regarding limiting the use of oral ketoconazole because of the risk of liver injury^{10,11}. It is understood that the TGA are currently reviewing information on oral ketoconazole to determine whether any action needs to be taken. These off-label treatment options are used despite the lack of robust data regarding the effectiveness of these therapies and potentially significant toxicities because of the severe physical and psychological symptoms associated with uncontrolled Cushing's disease. Thus pasireotide fulfils an unmet medical need in these patients where there is currently no approved

¹⁰ Press Release: European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole EMA/458028/2013 26 July 2013; http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001855.jsp&mid=WC0b01ac058004d5c1

¹¹ Safety Announcement: FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems; 7-26-2013 <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362444.pdf>.

medical therapy. Pasireotide has a safety profile that is consistent with the known adverse effects of approved somatostatin analogues (SSA) with the exception of an increased risk of hyperglycaemia.

Hyperglycaemia is a well-documented adverse effect of SSAs, and dysglycaemia (hyperglycaemia/hypoglycaemia) events have been reported as adverse reactions for octreotide and lanreotide. Study SOM230B2124 in HV corroborated that the underlying mechanisms of hyperglycaemia following pasireotide sc treatment in humans was mainly due to decreased insulin secretion and reduced GLP-1/GIP incretin response with no changes in hepatic or peripheral insulin sensitivity. Co-administering pasireotide with four different classes of antihyperglycaemic drugs (biguanide [metformin], insulin secretagogue [nateglinide], DPP-4 inhibitor [vildagliptin], and GLP-1 analogue [liraglutide]) for one week suggested that incretin based therapies (that is, GLP-1 analogues and DPP-4 inhibitors) would be most useful in the management of pasireotide-induced hyperglycaemia. In view of the pre-existing insulin resistance in patients with Cushing's disease, combination therapy with a biguanide (for example, metformin) and an incretin enhancer may also be appropriate to treat pasireotide-induced hyperglycaemia. This data was further corroborated by the pivotal Phase III Trial B2305 which showed that pasireotide induced hyperglycaemia was more likely to occur in patients with conventional risk factors for hyperglycaemia and metabolic syndrome (overweight/obese, hypertension, dyslipidemia, glucose intolerance/ diabetes mellitus) were more likely to have hyperglycaemia during this study. In this trial, the initial increase in FPG (peaking at Month 1) was followed by stabilisation or decreases in FPG levels after Month 3 in both the 600 µg and 900 µg dose groups. HbA1c increased within two months and remained stable for the duration of the study with mean HbA1c values at Month 12 being consistent with values seen at Month 2 (mean HbA1c values (SD) for the 600 µg and 900 µg groups, respectively at baseline were 5.83 (0.78) and 5.76 (0.79), at Month 2 were 7.24 (1.65) and 7.41 (1.5) and at Month 12 were 7.25 (1.32) and 7.21 (1.6)). Overall, 6.2% of patients (4.9% on 600 µg and 7.5% on 900 µg) discontinued due to hyperglycaemia related AEs. These data suggest that in Study B2305 pasireotide induced hyperglycaemia was manageable by approved therapies for diabetes. To further understand the appropriate management of pasireotide induced hyperglycaemia, Novartis will be conducting a post marketing study to compare the efficacy and safety of commonly available anti-diabetic therapies for the treatment of pasireotide induced diabetes.

Overall, pasireotide has a favourable benefit/risk profile in Cushing's disease. Because UFC levels decrease within the first months of treatment in patients who respond, patients who are not likely to achieve an optimal benefit-risk outcome with pasireotide can be identified early, thereby giving the option of early discontinuation of patients not likely to derive benefit from this drug. The proposed labelling fully characterises both efficacy and safety to enable appropriate use of pasireotide to maximize benefit while minimising risks to patients.

Questions on post-marketing studies

What post-marketing studies planned to assess the management of pasireotide induced hyperglycaemia and diabetes.

Response

As Post-Approval Measure in Europe and Post-Marketing Requirement in US, Novartis is currently planning a study to evaluate the effect of pro-active anti-diabetic intervention on hyperglycaemia associated with pasireotide treatment. Study SOM230B2219 is "A multi-centre, randomised, open-label, Phase IV study to investigate the management of pasireotide-induced hyperglycaemia with incretin based therapy or insulin in adult patients with Cushing's disease or acromegaly". Approximately 133 adult patients (age ≥ 18 years) (66 in Cushing's disease and 67 in Acromegaly) are planned to be enrolled.

The purpose of this trial is to investigate the optimal management of pasireotide-induced hyperglycaemia in patients with Cushing's disease or acromegaly in the overall population. The study aims to demonstrate that pasireotide-induced hyperglycaemia can be effectively and safely managed in majority of patients, including those with diabetes at start of pasireotide treatment. The primary objective is to evaluate the effect of treatment with incretin based therapy versus insulin on the 16-week glycaemic control in patients with Cushing's disease or acromegaly who develop or worsen hyperglycaemia on pasireotide, and cannot be controlled by metformin alone or other background anti-diabetic treatments. If previously normo-glycaemic patients experience increases in their fasting blood glucose based on pre-defined glycaemic criteria while on pasireotide, they will start anti-diabetic treatment using metformin. If they continue to experience increases in their fasting blood glucose within the first 16 weeks, they will be randomised in a 1:1 ratio to receive treatment with incretin based therapy (sitagliptin followed by liraglutide) or insulin for approximately 16 weeks.

Are any registry/database studies planned to describe patterns of use of pasireotide and outcomes of use?

Response

As a Post-Approval Measure in Europe and Post-Marketing Requirement in US, Novartis is conducting Study CSOM230B2410, a non-interventional, multinational, multi-centre post-marketing study for the generation of long term safety and efficacy data of pasireotide sc in patients with Cushing's disease (FPFV: 28 March 2013). Study CSOM230B2410 is also an additional pharmacovigilance activity listed in the Pharmacovigilance Plan of Signifor RMP. Approximately 100 sites in about 35 countries will participate in this study. The study will enrol up to 200 patients but not less than 100 patients. The patient population will consist of male and female patients aged 18 years or older with a diagnosis of Cushing's disease who are prescribed commercial pasireotide sc medication. The overall treatment pattern with pasireotide sc should be consistent with the local prescribing information. For this study, each enrolled patient will be followed up for three years after enrolment. Patients who permanently discontinue pasireotide sc prior to completing the three-year observation period will be followed up for three months after the last dose of pasireotide sc. The primary objective is to document the long-term safety and tolerability profile of pasireotide sc when administered as monotherapy or in combination with other therapies in patients with Cushing's disease. The endpoint for the primary objective is incidence of pasireotide sc-related AEs and SAEs during the three-year observation period. The timeframe of three years will allow to investigate the long-term safety/tolerability and efficacy of pasireotide sc including important safety evaluation on pasireotide sc (that is, induced glycaemia effects), as well as the long-term changes of pituitary hormones and their by-products. The three year observation period is long enough to allow for the stabilisation of the biochemical measures of disease activity (that is, UFC and plasma ACTH), thus reducing the confounding effect of acute changes in UFC on the long-term safety measures (such as glycaemia, and pituitary hormones).

Proposal for conditions of registration:

Novartis agrees to the conditions for registration put forward by the Delegate.

Concluding remarks

Novartis welcomes the Delegate's recommendation to approve Signifor for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. Patients with Cushing's disease have high morbidity and mortality rates and a significantly reduced quality of life. For patients who fail pituitary surgery, or for whom surgery is not an option, treatment options are limited. Pasireotide is the first pituitary-targeted medical therapy to demonstrate efficacy by directly addressing the

underlying mechanism of Cushing's disease (that is, suppression of increased ACTH secretion), with associated clinically relevant decreases in cortisol levels measured in serum, saliva and urine that are rapid, robust and sustained with longer follow-up (> two years). Additionally, clinically relevant improvements in signs and symptoms of hypercortisolism, such as BP, weight, BMI and cholesterol levels, were observed even in patients without complete normalisation of UFC, and patients experienced improvements in their Cushing's disease-related quality of life.

The safety profile of pasireotide was well characterised in the pivotal study as well as in the preclinical data and is consistent with the known class effects of somatostatin analogues. Hyperglycaemia is the most clinically relevant AE associated with pasireotide treatment. Given the recent improved understanding both of the underlying mechanism of hyperglycaemia and potentially effective treatment options, hyperglycaemia should be manageable in the clinical setting. Furthermore, hyperglycaemia associated with pasireotide is readily reversible upon discontinuation of treatment. The proposed labelling fully characterizes both efficacy and safety to enable appropriate use of pasireotide to maximise benefit while minimising risks to patients. The data provided in this application and the full characterisation of these data in the label support the use of pasireotide in the proposed indication.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Signifor solution for injection containing 300 µg/mL, 600 µg/mL, 900 µg/mL of Pasireotide (as diaspartate) to have an overall positive benefit-risk profile for the proposed indication;

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

In addition, the delegate requested ACPM advice on the following specific issues:

1. The proposed Australian PI recommends a starting dose of 900 µg, with titration back to 600 µg based on response and tolerability. Only the 900 µg dose was statistically significant versus the pre-specified threshold of at least 15% of patients achieving normalisation of their urinary free cortisol at six months. However, differences on efficacy endpoints, compared to the 600 µg dose, were not striking; differences on safety endpoints were also not striking. Would it be better to recommend a starting dose of 600 µg with possible up-titration to 900 µg? (As in EU, see Table 1.) Alternatively, should the PI just recommend a dose range of 300 µg-900 µg? (As in US, see Table 1.)

With regard to starting dose, the ACPM advised the evidence suggests that 900 µg BD would appear to be too high as a starting dose and the PI could recommend a dose range of 300-900 µg or alternatively a starting dose of 600 µg.

2. Pasireotide is eliminated via hepatic excretion. Relative to patients with intact hepatic function, patients with mild, moderate, and severe hepatic impairment (Child-Pugh A, B, C) show a 12%, 56%, 42% increase in AUC_{inf}, and a 3%, 46%, 33% increase in C_{max} (Study B2114). Based on these data, the proposed PI recommends dose adjustment in patients with moderate hepatic impairment and contraindication of pasireotide use in patients with severe hepatic impairment. Do the data (or expert clinical opinion)

support such a recommendation? Is the general advice about liver monitoring for patients without hepatic impairment adequate? (Prior to treatment; after one to two weeks, after two to three months; and then as clinically indicated)

Based on the data on hepatic impairment the proposed PI recommends dose adjustments in patients with moderate hepatic impairment and contraindication with severe hepatic impairment. This seems reasonable, as does liver monitoring for patients without hepatic impairment.

3. In the context of the seriousness of Cushing's disease, are the adverse effects manageable? In particular, can hyperglycaemia (which is seen almost immediately with increases in fasting plasma glucose noted within two weeks) be managed?

Pasireotide appears to be a useful treatment, but the treatment effect is modest and accompanied by a constellation of adverse effects. Hyperglycaemia will be manageable in most patients. Close monitoring and individual dose adjustment will be important to assess response to treatment. Pharmacovigilance procedures will be necessary to collect further data on safety.

Proposed conditions of registration:

The ACPM agreed with the delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory negotiation of the Risk Management Plan most recently approved by the TGA,
- Negotiation of Product Information and Consumer Medicine Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Signifor solution for injection containing 300 µg/mL, 600 µg/mL, 900 µg/mL of Pasireotide (as diaspertate), indicated for:

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

Specific conditions applying to these therapeutic goods

Signifor (pasireotide) Safety Risk Management Plan (RMP in EU-RMP format) Version 2 dated 13 January 2012 (data lock point 17 November 2011) with Safety Risk Management Plan Australian Implementation Version 2 dated 21 September 2012, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1: Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2: Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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<http://www.tga.gov.au>