Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for Somatropin

Proprietary Product Name: Zomacton

Submission No: 2008-2954-5

Sponsor: Ferring Pharmaceuticals Pty Ltd

December 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation (New Strength/New mode of administration)
Decision:	Approved
Date of Decision:	3 September 2010
Active ingredient(s):	Somatropin
Product Name(s):	Zomacton
Sponsor's Name and Address:	Ferring Pharmaceuticals Pty Ltd PO Box 135, Pymble, NSW 2073.
Dose form(s):	10 mg power for injection
Strength(s):	10 mg per vial
Container(s):	Colourless 4 ml glass vials, glass type I[1] with rubber closures used in combination with an aluminium seal and a plastic cap.
Pack size(s):	Zomacton 10 mg powder for solution for injection is supplied with a m-cresol preserved solvent filled into glass syringes and adaptor (1 mL), singles.
Approved Therapeutic use:	For the long term treatment of children who have growth failure due to inadequate secretion of growth hormone.
Route(s) of administration:	Subcutaneous (SC) injection
Dosage:	[Abridged]. Zomacton dose must be individualised for each patient. A dosage schedule of up to 0.1 mg/kg body weight administered three times weekly by subcutaneous injection is recommended. As an alternative, a dose of 0.17- 0.23 mg/kg bodyweight per week divided into 6-7 subcutaneous injections is recommended. The total weekly dose of 0.27 mg/kg or 8mg/m^2 should not be exceeded.
ARTG Number (s)	156226 (10mg)

Product Background

Ferring Pharmaceuticals Pty Ltd has submitted an application to register an additional strength of Zomacton (10 mg; containing somatropin as the active ingredient) and to propose/update a combined Product Information (PI) document for the new 10 mg presentation and the currently registered 4 mg presentation. Zomacton 10mg is intended to be administered subcutaneously (SC) either via a conventional syringe or through the ZomaJet needle free injector device. The use of Zomacton by a needle free device is the first somatropin submission that involves injection via a needle free device. Upon reconstitution for SC injection, the new strength is 3-times higher than the current one (that is, 10 mg/mL compared to 3.3 mg/mL). No change to the currently registered indication is proposed.

Zomacton (4 mg) was previously known as Scitropin until the sponsorship was transferred from Scigen to Ferring in 2007. The Australian Drug Evaluation Committee (ADEC, now succeeded by the Advisory Committee for Prescription Medicines (ACPM)) considered an application to register Scitropin lyophilised powder for subcutaneous injection (with diluent)

[1] Type I according to European Pharmacopeia.

at its 183rd meeting and recommended approval for the long term treatment of children who have growth failure due to inadequate secretion of growth hormone.

Regulatory Status

An application to register the 10 mg strength was lodged in Europe in 2008.

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

Same as currently registered lower strength product.

Manufacture

The active pharmaceutical ingredient (API) is to be sourced from a new manufacturing site. There has been no change in the plasmid used to produce the drug substance.

Physical and Chemical Properties

No new data were supplied with respect to product-related impurities.

Specifications

Release and Shelf-life specifications for bulk lyophilised somatropin were evaluated and found to be acceptable.

Stability

Data are sufficient to establish a shelf life of 36 months at -70^{o}C for somatropin active manufactured at the new site.

Drug Product

Formulation

One vial with powder for solution for injection contains somatropin, mannitol disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and nitrogen.

An overfill of 5% is added during manufacturing. The overfill compensates for losses during extraction of the reconstituted solution and allows for withdrawal of the labelled amount of 10 mg somatropin.

One syringe with 1 mL solvent for solution for injection contains m-cresol and Water for injection.

Manufacture

The common methodology for lyophilised vial preparation for a temperature sensitive substance is applied. It involves the dissolution of the drug substance and excipients, followed by sterilisation by filtration. The product is then aseptically filled and freeze-dried before being stoppered under controlled conditions.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were evaluated and it was considered that appropriate validation data have been submitted in support of the test procedures.

Stability

Based on the results obtained in the stability studies, the following shelf-life and storage conditions are considered justified for the drug product:

The overall shelf-life for the composite pack is two years when stored at 2°C – 8°C (in a refrigerator).

The reconstituted solution is stable for 28 days when stored at 2°C – 8°C (in a refrigerator).

Bioavailability

There are no outstanding issues.

Bioengineering (device)

After comments from an external clinical evaluator, including:

1. Whether there were any differences in variously named device prototypes during Zomacton clinical trials.
2. References to different delivery head configurations.
3. General concern over whether device performance had been assessed by the TGA,

the Biomaterials and Engineering Section of the Office of Laboratory and Scientific Services (OLSS) was asked to comment on the associated needle-less injector design, function and performance.

The needleless injector is included in the Australian Register of Therapeutic Goods (ARTG) and thus already available for supply in Australia, a process that does not require in-depth technical evaluation by the TGA. However, the law requires that a Technical File be maintained by the manufacturer and that this be provided to the TGA on demand. The sponsor was asked (August 2009) to provide the Technical File for the needle-less injector and examples of the device as well as vials filled with water for demonstration purposes. The sponsor confirmed that the variously named device prototypes are either identical or not significantly different to the device that is already included in the ARTG.

The delivery head comes in three orifice sizes. Which orifice size to use is a compromise between discomfort during injection and incomplete (wet) injections. The user is instructed to use heads with the smallest diameter that does not lead to a high frequency of incomplete injections.

The material provided in the Technical File was complete and found to be acceptable.

Examples of the device were examined and tested by the TGA. These were found to work normally and as expected.

While the needle-less injector is more complicated to use than a conventional syringe, comprehensive instructions are provided, and the user is expected to receive training on its use. Further, there are several markings on the device itself that provide prompts for setting up and making an injection.

There are no concerns about approving the product in relation to device design and performance.

Labelling, packaging and documentation

The carton and vial labelling is satisfactory for the Zomacton 10 mg strength. The PI/Consumer Medicine Information (CMI) recommendation for storage of reconstituted solution is supported by stability data.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data submitted in support of this application have been evaluated in

accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Issues of concern

None.

III. Nonclinical Findings

Introduction

Two local tolerance studies were submitted with the current Australian submission. These studies were Good Laboratory Practice (GLP)-compliant, and designed and conducted in accordance with the relevant European Union (EU) guideline (CPMP/SWP/2145/00). Both included histopathological analyses.

Pharmacology

No new data submitted.

Pharmacokinetics

No new data submitted.

Toxicology

Local tolerance

Single- and 4-week repeat-dose SC local tolerance studies were performed in pigs. Both studies used the newly proposed strength (10 mg/mL) of Zomacton. Administration was by the ZomaJet needle-free injection system in the repeat-dose study, and by both the ZomaJet injector and by conventional hypodermic needle in the single-dose study. Zomacton is to be used in paediatric patients and young and/or juvenile pigs were used in the submitted studies. The pig is an appropriate animal model to assess local tolerance due to similarities between the skin of pigs and humans (particularly in regard to structure, thickness and lack of hair).

The maximum recommended human dose of somatropin is 0.1 mg/kg per injection (when treatment is 3-times weekly) or 0.039 mg/kg per day (for a total weekly dose of 0.27 mg/kg); in children in the body weight range 10–50 kg, this equates to maximum doses of 1–5 mg per injection and 0.39–2 mg per day. These doses are comparable to those employed in the animal studies (1 or 2 mg/day).

Injection site reactions following SC administration of a single 1 mg dose of Zomacton 10 mg to juvenile pigs comprised minimal to slight inflammatory changes consistent with injection trauma only. Administration by the ZomaJet injector and by the hypodermic needle were equally well tolerated.

In the repeat-dose study, juvenile (6 weeks old) and young animals (3.5 months old) were administered Zomacton 10 mg at SC doses of 1 and 2 mg/day in the respective age groups, or vehicle only, once daily for 28 days using the ZomaJet injector. Swelling and redness were usually observed immediately after injection. These effects were more frequent and more severe at Zomacton 10 mg treated sites compared to vehicle-treated sites (although only to a limited degree), and also greater in young animals compared to juvenile animals (consistent with the larger injection volume used in the older animals). Swelling and reddening usually resolved within 24 h. Microscopic findings were generally similar at vehicle- and Zomacton-treated sites, although a number of changes were observed only with Zomacton treatment. These were focal hyperkeratosis, mononuclear cell infiltration in the dermis and/or subcutis, ulceration, dermal oedema and serous atrophy of the subcutaneous fatty tissue, all of which were minimal in severity, except for mononuclear cell infiltration, which was considered minimal-moderate. The latter three findings were observed in young, but not juvenile animals

(that is, with dosing at 2 but not 1 mg). The microscopic lesions were absent or less frequent/severe at injection sites used earlier in the study, indicating reversibility.

Nonclinical Summary

- Nonclinical data in the current Australian submission comprised two local tolerance studies with the new 10mg/mL strength in juvenile or young pigs, involving single or repeat-daily (28 days) SC administration. The studies complied with GLP and were performed in accordance with the relevant EU guideline.

- The single-dose study demonstrated that injection of a 1 mg dose of Zomacton 10 mg was well tolerated in juvenile pigs. There was no difference in local tolerance between injection via the ZomaJet device or by conventional hypodermic needle.

- The 28-day repeat-dose study involved daily SC administration of a 1 mg dose in juvenile pigs and 2 mg in young animals using the ZomaJet injector. Treatment with Zomacton 10 mg was associated with an increase in the incidence and severity of mononuclear cell infiltration at the injection site (up to moderately severe, but usually slight) and focal hyperkeratosis (minimal) at both dose levels, as well as ulceration and dermal oedema (single instances and minimally severe) and serous atrophy of the subcutaneous fatty tissue (minimal) at the higher dose only. These local changes were reversible.

Conclusions and Recommendations

SC administration of Zomacton 10 mg was well tolerated in pigs. There are no nonclinical objections to registration of Zomacton 10 mg.

IV. Clinical Findings

Introduction

The sponsor sought to demonstrate that:

- the new formulation for SC injection was bioequivalent to the currently registered formulation, and
- the two modes of administration were bioequivalent for both formulations.

The clinical part of the current Australian submission included 2 bioequivalence studies (FE999905 CS001 and ZMJ 101) and 1 local tolerability study (FE999905 CS002).

Pharmacokinetics

Study FE999905 CS001

This study compared single doses of the following 3 treatments:

> (A) Zomacton 4 mg registered product, 1.67 mg (5 IU), administered SC by conventional syringe.
>
> (B) Zomacton 10 mg new product, 1.67 mg (5 IU), administered SC by conventional syringe.
>
> (C) Zomacton 10 mg new product, 1.67 mg (5 IU), administered by ZomaJet.

The sponsor declared that the 4 mg and 10 mg formulations used in the study were identical to those which are the subjects of the present application.

The primary objectives of the study were to compare bioavailability, in terms of area under the concentration versus time curve (AUC) and maximum serum or plasma concentration (C_{max}).

According to the clinical study report (CSR), the acceptance range for bioequivalence had been set at 80-125% based on the usual ratios of AUC and C_{max} values derived from log-

transformed data (see European Medicines Evaluation Agency (EMEA) 2001[2]). It was planned to study 24 subjects. This number was calculated using an estimated coefficient of variation 0.085 derived from another company study (the "Novum" study), on the basis of a requirement for 80% power to demonstrate equivalence.

Subject inclusion criteria included: healthy, non-smoking, male aged 23-55 with body mass index (BMI) in the range of 19-29.

The CSR stated:

> "Test injections with the ZomaJet were performed at screening, using normal saline (NaCl 0.9%). The test injections were performed to select the optimal ZomaJet head for study drug administration for each subject. The optimal ZomaJet head was used for the administration."

Subjects were admitted to the study unit on the evening before dosing and remained there until approximately 24 hours post-dose. Subjects had to fast from 10 hours before dosing until 1 hour after. Times of dosing were between 8 and 9 am.

Blood samples for hGH measurement were drawn 1 hour pre-dose, and then 0.5-4 hourly until 24 hours post-dose. About half of the 20 h observations and more than half of the 24 h observations were below the limit of quantification.

Results

The bioequivalence assessment was done using values derived from an Analysis of Variance (ANOVA) model which included formulation, period, subject within sequence and sequence as sources of variation. Bioequivalence outcomes were as tabulated below (Table 1).

Table 1.

Parameter	Ratio	90% CI
	(B) New product, by syringe / (A) Reference	
AUC	1.04	[0.99, 1.09]
C_{max}	1.04	[0.94, 1.15]
	(C) New product, by ZomaJet / (A) Reference	
AUC	1.11	[1.06, 1.16]
C_{max}	1.21	[1.11, 1.32]

The available data do not settle the question of the frequency of incomplete administration of the study medication by the new device, although the fact that the standard deviation of AUC values was less with treatment C than with treatment B provides some reassurance. Examination of individual subject AUC values shows that in 15/24 cases, AUC was greater with treatment (C) than treatment (B). In the 9 cases where this was not so, the ratio AUC(C)/AUC(B) ranged from 0.86 to 0.99.

Some pharmacodynamic measurements were also made. The three treatments resulted in very similar mean serum free fatty acid (FFA) and insulin-like growth factor-1 (IGF-1) concentrations.

Safety

Local tolerance

[2] Committee for Proprietary Medicinal Products (CPMP), the European Agency for the Evaluation of Medicinal Products (EMEA). *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*. 2001. www.tga.gov.au/docs/pdf/euguide/ewp/140198entga.pdf

All three formulations investigated were well tolerated. No subject experienced induration, pain or other symptoms. Five subjects showed local reactions, two after Treatment A and three after Treatment C.

> Treatment A (Zomacton 4 mg, syringe administration): one subject showed erythema (size 20 mm), at 15 min after injection; another subject showed erythema (size 3 mm), also after 15 min. Both subjects showed no local reactions at the next scheduled observation time at 1 h.
>
> Treatment C (Zomacton 10 mg, ZomaJet administration): one subject showed erythema (size 20 mm) at 15 min after injection; another subject showed erythema (size 10 mm), and oedema (size 7 mm). Both reactions were observed at the scheduled observation time 15 min after injection. A third subject showed erythema (size 5 mm) at 15 min after injection.
>
> In all cases, the local reactions had disappeared at the next scheduled observation time 1 h.

After administration of Treatment C, minimal back flow of the study medication (skin moisture) was seen in two subjects.

Adverse events (AEs)

No serious AEs were reported, and no subject was withdrawn because of an AE. Headache (n=3), injection site reaction (n=1), cough (n=1), hot flushes (n=1), dysaesthesia (n=1), herpes simplex (n=1), pharyngitis (n=1), nausea (n=1) and vomiting (n=1) were reported.

Comment

The study appears to have been carefully conducted.

Bioequivalence of the registered and the new products was established using the usual criteria. However, use of the new injection device does not appear to result in equivalent levels of plasma hGH. The AUC ratio, but not the C_{max} ratio, met the criteria for bioequivalence. The sponsor argues (CSR) that the difference in C_{max} is of no clinical significance, and the clinical evaluator was inclined to accept this argument in the case of a product for parenteral administration - that is, that although the two administration devices do not result in strictly bioequivalent doses, the fact that absorption appears to be slightly faster with the ZomaJet is of no consequence. **Study ZMJ 101**

This study compared single doses of the following 2 treatments:

> (A) Somatropin, 1.67 mg (5 IU), administered SC by "Medi-Jector".
>
> (B) Somatropin, 1.67 mg (5 IU), administered SC by conventional syringe.

This study used the registered 4mg formulation of Zomacton. The sponsor's letter of application (dated 30 September 2008) indicated that the Medi-Jector device used in the study was comparable to the device which is a subject of the present application.

The aim of the study was "to investigate and compare the pharmacokinetics of recombinant deoxyribonucleic acid (rDNA)-hGH after single administration using the Medi-Jector and conventional subcutaneous injection."

Subject inclusion criteria included: healthy, male, aged 20-45, weight within specified limits, smoking ≤ 15 cigarettes daily.

The bioequivalence criteria were stipulated as for Study FE999905 CS001, above.

The study protocol stipulated that 12 subjects would participate, whereas 14 did so. 4 of the subjects did not complete the study routinely:

One subject was withdrawn in the first study period "for personal reasons", and “replaced on the same day" by another subject. It is also reported that 4 subjects, due to "incomplete administration of the study medication using the Medi-Jector", were "temporarily withdrawn". Two of these subjects "repeated the study period after one week washout" (although the study protocol does not appear to provide for any such option), but the "other two subjects refused to participate any further for personal reasons".

It was stated that subjects stayed in the research facility for approximately 40 h (16 hours before and 24 hours after drug administration) during each study period; that administration was at approximately 8 am; and that "On the evening of admission the Medi-Jector was tested for each subject using the right upper arm."

The protocol does not stipulate pre-dose fasting, but methyl-xanthines were prohibited. Blood samples for hGH measurement were drawn pre-dose, and 0.5-4 hourly until 24 hours post-dose.

Results

Bioequivalence outcomes were as tabulated below (Table 2), using values derived from an Analysis of variance (ANOVA) model.

Table 2.

Parameter	Ratio	90% CI
	(A) Medi-Jector / (B) Syringe	
AUC	0.98	[0.93, 1.03]
C_{max}	1.24	[1.08, 1.42]

Safety

No serious AEs were reported, and no subject was withdrawn because of an AE. AEs reported included drowsiness (n=2), pain in right arm (n=1), skin lesions at injection site (n=2), haematoma at injection site (n=1), nausea after venopuncture (n=1), urinary tract infection (n=1), headache (n=1) and vomiting.

Drug Interactions

No specific studies submitted.

Pharmacodynamics

Some pharmacodynamic data were collected in studies FE999905 CS001 and ZMJ 101, but these data were of little relevance to the application.

Efficacy

No new data submitted.

Safety

Study FE999905 CS002

This was an open study of local tolerability of Zomacton 10 mg administered by "ZomaJet Vision X" in individualised dosages to patients over 12 weeks.

Inclusion criteria included: Diagnosed GH deficiency or Turner's syndrome, otherwise healthy; age 3-17; has received growth hormone (GH) replacement therapy for ≥ 6 months.

Before treatment start, instruction was given on the use of the device (for example by injecting into an orange).

Three different head sizes (A, B, C) were available for ZomaJet Vision X. All subjects started by using head A for the three initial transjections (one per day). If two out of three transjections were incomplete (as evidenced by a drop of liquid remaining at the transjection site, or liquid running from the site), the subject was to switch to head B. If two out of three transjections with head B were incomplete, the subject was advised to contact the clinic. If use of the device was correct, subjects were to switch to head C. In order to maintain transjection quality, every ZomaJet Vision X head was only used for a maximum of 7 injections. Thereafter the head was replaced with a new one.

Transjections were to be done each evening, on one side of the body (leg, buttocks or abdomen), opposite to the side of the body used for administering growth hormone prior to entering the study. If the subject used both sides prior to study entry, one side was to be chosen by the investigator by use of best clinical judgement. Visits to the clinic took place at screening/treatment initiation (V_0), after 2 weeks (V_2), 6 weeks (V_6), and 12 weeks (V_{12}), of treatment. At each visit, the investigator assessed local tolerability reactions in the area used for transjections. Photos of the area used for transjections were taken for central assessment by a dermatologist. At each visit all reactions were counted, potentially including any reactions that were counted at the prior visits. Thus at each visit the accumulated occurrences were counted. At Visits V_0, V_2 and V_6, the daily transjection was done at the clinic. The study investigator assessed immediate local reactions and the subject assessed the pain and itching associated with the transjection. Following V_0, visits to the clinic for proper instruction in use of ZomaJet Vision X were offered as needed. At Visits V_2, V_6 and V_{12}, subjects were asked to report any unusual transjection-related experiences occurring in the week prior to the visit.

Results

At one centre, there was a major protocol violation, in that the 6 patients investigated there administered transjections to both sides of the body.

One subject out of 27 was withdrawn as a result of an unacceptable transjection-related local tolerability reaction (application site pain, reported at V_0 and reiterated at V_2). The local and central assessments of transjection reactions are shown in Table 3. Only one reaction was graded severe: a case of bruising, in the local investigator's assessment at V_2. Immediate transjection reactions, assessed by the local investigator at V_0, V_2 and V_6 are shown in Table 4. The proportion of subjects experiencing no pain increased by visit. Only one subject reported transjection-related itching during the study at one visit.

Table 3. Transjection site reactions. Study FE999905 CS002

Reaction	Local assessment (numbers) (N=27)								Central assessment (numbers) (N=27)							
	V_0		V_2		V_6		V_{12}		V_0		V_2		V_6		V_{12}	
	S*	E*	S	E	S	E	S	E	S	E	S	E	S	E	S	E
Punctate haemorrhage	5	7	10	19	13	28	15	41	6	7	11	23	16	44	13	38
Bruising	4	4	13	16	9	21	16	31	4	12	10	22	12	24	15	48
Inflammation - diffuse	0	0	2	2	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation - nodular	0	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0
Change in pigmentation	3	3	4	6	4	8	5	14	0	0	0	0	0	0	0	0
Dermal atrophy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lipo-dystrophy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sclerosis or scar formation	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0

*S=Subjects; E=Events

Table 4. Immediate transjection site reactions. Study FE999905 CS002

Visit	Timepoint	Punctate haemorrhage	Redness	Diffuse dermal swelling
V_0 n=27	0 minutes	17	11	1
	15 minutes	12	13	3
	60 minutes	10	9	2
V_2 n=27	0 minutes	20	12	3
	15 minutes	11	13	4
	60 minutes	7	4	2
V_6 n=26	0 minutes	14	8	0
	15 minutes	15	9	1
	60 minutes	8	1	1

Comment

No significant matters relating to local tolerance have emerged. In the circumstances (where a patient always has the option of reverting to conventional syringe administration), the clinical evaluator thought the local tolerance data are adequate.

Post marketing experience

No data.

Clinical Summary and Conclusions

The new formulation

In the clinical evaluator's opinion, study FE999905 CS001 demonstrates adequately that the Zomacton 10 mg product is bioequivalent to the existing product, when administered by syringe.

The new transjection device

The clinical evaluator has some concern about the possibility of incomplete administration of doses, although this does not appear to have been a problem in study FE999905 CS001. This question should be raised with whoever is evaluating the actual ZomaJet device and associated patient instruction material.

Subject to this, the clinical evaluator believed studies FE999905 CS001 and CS002 provide adequate justification for use of the new device as an alternative method of administering the new formulation.

V. Pharmacovigilance Findings

Risk Management Plan

There was no Risk Management Plan (RMP) submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

All chemistry and quality control issues have been resolved.

The quality evaluator and the clinical evaluator both discussed the bioavailability study, **CS001.** The following table (Table 5) is extracted from the summary which shows bioequivalence of the proposed formulation with registered product using a conventional syringe.

Table 5.

Treatments		**Parameters Compared**	**Point Estimate**	**90% CI**
B: Zomacton 10 mg by Syringe	**A**: Zomacton 4 mg by Syringe	AUC_{0-t}	1.05	0.99 - 1.10
		Cmax	1.04	0.94 - 1.15
Treatments		**Parameters Compared**	**Point Estimate**	**90% CI**
C: Zomacton 10 mg by ZomaJet	**A**: Zomacton 4 mg by Syringe	AUC_{0-t}	1.11	1.05 - 1.16
		Cmax	1.21	1.10 - 1.31

However, the clinical evaluator mentions that " the administration of Zomacton 10 mg by the ZomaJet (Treatment C) is not bioequivalent to the administration of Zomacton 4 mg (Treatment A) by conventional syringes because the upper Confidence Interval (CI) limit (1.31) of C_{max} is over 1.25". The sponsor justifies this by stating that this has been observed in several published studies using needle free devices; the higher C_{max} values are not reflected in any measured pharmacodynamic biomarkers (IGF-1). The similar AUCs indicate that the exposure and effect in similar with needle free devices and conventional injections.

A sheer stress study showed that the device delivers expected hGH protein without detectably altering the composition of the product.

It is stated by the TGA's device evaluator that there is accuracy in the dose delivered; other aspects of device design and performance are also considered to be acceptable for registration. The device evaluator mentions that samples of the device were examined and tested by the TGA and were found to work "normally and as expected". There are no concerns about the product in relation to device design and performance. The evaluator mentions that the device is complicated when compared with syringes; however, the instructions are "well laid out and comprehensive" and recommended approval for a design perspective. The device is currently on the Register.

The shelf life for the finished product is 2 years when stored at 2^0C-8^0 C (in a refrigerator). The reconstituted solution is stable for 28 days when stored at 2^0C-8^0 C (in a refrigerator).

The Pharmaceutical Subcommittee (PSC) of ACPM recommended approval from a chemistry perspective. All issues raised by PSC have been satisfactorily addressed by the sponsor.

Nonclinical

The current submission consisted of two local tolerance studies. These studies used the proposed new strength 10mg/mL in juvenile or young pigs involving single or repeat daily SC injection. ZomaJet was used in the repeat dose study and both ZomaJet and the conventional hypodermic needle were used in the single dose study.

The maximum recommended human dose was used in these studies. The doses were comparable to those used in other animal studies.

In the repeat dose study, swelling and redness were observed in those administered ZomaJet as well as the conventional SC injection. These events disappeared within 24 hours. There were other local changes (focal hyperkeratosis, dermal oedema, ulceration, serous atrophy) usually minimal in severity and reversible. Some amendments to the PI were recommended. There were no nonclinical objections to registration.

Clinical

In essence, the studies submitted with the current Australian submission sought to demonstrate that the new formulation was bioequivalent to the currently registered formulation. The studies also sought to demonstrate that the two modes of administration (subcutaneous injection and needleless device) were bioequivalent for both formulations.

There were three studies submitted. Two were bioequivalence studies (**CS001** and **ZMJ 101**) and one was a local tolerability study.

Study CS001 compared single doses of the following treatments: Zomacton 4 mg registered product administered subcutaneously by conventional syringe; Zomacton 10 mg new product administered sc by conventional syringe; Zomacton 10 mg new product administered by ZomaJet. These formulations are identical to the formulations relevant to the current submission.

It was planned to include 24 subjects. The clinical evaluator mentions that this number was calculated using an estimated coefficient of variation (0.085) derived from another company study (the "Novum" study), on the basis of a requirement for 80% power to demonstrate equivalence. Healthy, non-smoking males, aged 23- 55 and with a BMI in the range of 19-29 were recruited. The acceptance range for bioequivalence was set at 80-125% based on the usual ratios of AUCs, C_{max} values derived from log transformed data (EMEA 2001).

The results showed bioequivalence of the new formulation with the old when administered by the conventional needle and also by the proposed ZomaJet device. This is in relation to AUC. However, bioequivalence was not seen in relation to C_{max} where the upper limit of the 90% CI was reported as being 132% (and outside the pre-defined limit of 125%). The clinical evaluator accepts the sponsor's argument that the slightly increased rate of absorption is not clinically relevant. Despite this, the clinical evaluator has expressed concerns regarding the new device. The main concerns are:

a) Was bioequivalence affected by the choice of the head of the device?
b) The lack of clarity about how the device functions and how it is to be used.

In their response, the sponsor explains that the ZomaJet device is designed to deliver growth hormone under high pressure by a compressed spring. The pressure created results in ejection of the fluid through a micro-orifice of the device head at velocities sufficient to give an injection. There are three different size heads (A, B and C) which can be used with the device. They differ in the micro-orifice diameter (0.16mm, 0.23 mm and 0.28mm). The head to be used with the device is usually tested according to instructions using normal saline as injection. If a head is suitable then the injection will be "dry". Head A is tried first and then if found unsuitable, head B and then subsequently head C is tried. If head C is found unsuitable then the patient is unsuitable for this device. Once the optimal head is chosen the patient continues with the same head for all injections replacing the head after 7 injections.

The sponsor also states that the bioequivalence study demonstrates that, if administered correctly, it is "bioequivalent" to the conventional needle. Thus, it does not directly address the question of the clinical evaluator, which is, whether the head sizes affect bioavailability.

Study ZMJ 101: The study compared 1.67 mg administered SC by "Medi-Jector" versus somatropin (1.67 mg) administered by conventional syringe. The formulation used is identical to that which is proposed for marketing. The Medi-Jector device used was an earlier model that is directly comparable to the device proposed for marketing. The bioequivalence criteria were similar to those stipulated in the previous study.

Fourteen healthy adult male subjects participated in the study and bioequivalence was demonstrated in terms of AUC and C_{max}.

Based on the sponsor's response regarding the formulation this study provides evidence of bioequivalence of the proposed formulation versus registered formulation and the two methods of injection.

Safety:

CS001: The clinical evaluator mentions that all formulations were well tolerated. Two subjects had local reactions after treatment A (Zomacton 4 mg registered product). Three subjects had local reactions after transjection (treatment C). All three subjects reported erythema of varying size and one of these subjects had accompanying oedema. These were reported at 15 minutes post injection and were not present at the next scheduled observation time (1 hour).

Minimal black flow of the study medication was seen in two subjects using the needle-less device.

ZMJ 101: The safety findings were discussed in the CER and the clinical evaluator mentions that there were no serious adverse effects reported; no subjects were withdrawn because of adverse effects. With the Medi-Jector device there were four local reactions reported: 1 pain, 2- skin lesions at injection site and 1 haematoma.

Safety study CS002: This was an open study of the local tolerability of Zomacton 10 mg administered by ZomaJet Vision X over 12 weeks. Those who were GH deficient or had Turner's syndrome receiving replacement GH (aged 3-17) were eligible to participate. All three different head sizes (A, B or C) were available. The head sizes were changed from A to B to C if there was evidence of incomplete transjection. The subjects were reviewed fortnightly for tolerability reactions. Photographs were taken for central assessment by dermatologist. The clinical evaluator concludes that "no significant matters relating to local tolerance have emerged".

Recommendation by the clinical evaluator:

The clinical evaluator expresses concern on the potential for incomplete administration. The effect of the different heads on bioavailability is also a concern. If these issues are resolved, the clinical evaluator recommends approval of the new device as an alternative method of administering the new formulation.

The clinical evaluator recommends the approval of the new strength via the conventional syringe, based on study **CS 001**.

Risk Management Plan (RMP)

No RMP was submitted with this application.

Risk-Benefit Analysis

The Delegate agreed with the clinical evaluator that the new strength is registrable based on the data submitted.

In relation the use of the needle-less device, the following are issues of concern:

- The device evaluation confirms the accuracy of dose delivered. However, it has not been stated whether the size of the "head" would affect the bioavailability of the formulation. The bioequivalence study (CS 001) with 24 subjects is not ideal to ascertain this, due to the small number of subjects involved, especially when three different head sizes were used. The sponsor's response dated 4th Sept 2009 states that head A is acceptable for approximately 85% of the subjects. This implies that the other heads "B and C" were used in some subjects in the bioequivalence study. Was bioequivalence affected by the head sizes?
  The sponsor should provide the number using each head and the bioequivalence results for each group (A, B and C) in its pre-ACPM response.
- Another deficiency is that the bioequivalence study has been conducted in healthy male adults. The product is proposed in children who may have different skin type in terms of epidermal

thickness and other characteristics. Is the absorption affected by dry skin, eczematous skin and different sites of administration? Patients with childhood onset GH deficiency have been shown to have changes in their skin morphology[3]. Thus, the findings from healthy adult volunteers cannot be extrapolated to children with GH deficiency. A therapeutic equivalence study on the target population is required using the two methods of administration, to clearly establish efficacy.

- Minor differences in bioavailability may be overcome if efficacy or a surrogate of efficacy can be monitored after the administration of Zomacton. It would not be feasible to request regular monitoring of IGF-1 to ensure adequate efficacy. Also, lower bioavailability due to the use of an unsuitable head may lead to the loss of opportunity for maximal growth.

Proposed Action:

Thus, the Delegate is of the opinion that there are insufficient data on efficacy with the new mode of administration, the needle-less ZomaJet device and recommends rejection. A larger study is needed to determine therapeutic equivalence with the conventional injection in the target population.

The Delegate recommended approval of the new strength to be administered with the conventional injection.

The advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) was sought.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission from Ferring Pharmaceuticals to register the new strength of somatropin (Zomacton) powder for injection 10 mg and the new administration route of somatropin (Zomacton) powder for injection 4 mg and 10mg when administered with the ZomaJet device, for the indication:

> For the long term treatment of children who have growth failure due to inadequate secretion of growth hormone.

In making this recommendation, the ACPM noted the deficiency in the bioequivalence studies, however, the ACPM were satisfied that evidence of an appropriate risk benefit profile was sufficiently demonstrated for the target population.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zomacton somatropin 10 mg multidose powder for injection vial with diluent syringe and Zomacton somatropin 4 mg multidose powder for injection vial with diluent vial, for subcutaneous injection, indicated for:

> The long term treatment of children who have growth failure due to inadequate secretion of growth hormone.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

[3] Main K, Nilsson KO & Skakkebaek NE. Influence of sex and growth hormone deficiency on sweating, Scandinavian *Journal of Clinical and Laboratory Investigation* 1991 51 475-480.

PRODUCT INFORMATION
ZOMACTON® 4 mg and 10 mg
Somatropin (rbe)

NAME OF THE DRUG

ZOMACTON contains somatropin which is a protein having the structure (191 amino acid residues) of the major component of growth hormone produced by the human pituitary gland. It is produced in E.coli., by a method based on recombinant DNA technology.

DESCRIPTION

ZOMACTON is a sterile white lyophilised powder intended for injection after reconstitution. It is supplied with preserved diluent. The multidose vials are intended to be used for a single patient only. The composition of each strength of ZOMACTON and accompanying diluent is specified below:

	ZOMACTON 4 mg	ZOMACTON 10 mg
Powder	Somatropin 4 mg Mannitol 25.9 mg	Somatropin 10 mg Mannitol 10 mg Sodium phosphate - dibasic dodecahydrate 3.57 mg Sodium phosphate - monobasic dihydrate 0.79 mg
Diluent	Benzyl alcohol 45 mg Sodium chloride 45 mg Water for injections to 5 mL	Meta-cresol 3.3 mg Water for injections to 1 mL

PHARMACOLOGY

Pharmacodynamic properties of ZOMACTON are identical to human growth hormone. Human growth hormone stimulates linear growth and increased IGF-1 (Insulin-like growth factor/somatomedin-C) concentrations in children with growth hormone deficiency. The measurable increase in linear growth results from the effect of ZOMACTON on the epiphyseal growth plates of long bone. ZOMACTON is intended to supply the lack of naturally secreted hormone. Somatropin increases skeletal and cell growth in patients with growth hormone deficiency. It increases protein and carbohydrate metabolism.

CLINICAL TRIALS

A clinical study in 162 children showed an increase during 24 weeks to 24 months of treatment from an annualised growth velocity of 32 mm to 91 mm at 6 months, 83 mm at 12 months and 75 mm at 24 months. Seventy children were studied for 24 months and there are no data for final height. The dose administered was usually 0.1 mg/kg thrice weekly.

Pharmacokinetics following intravenous administration of 0.1 mg/kg ZOMACTON showed the elimination half life was about 25 minutes and the mean plasma clearance was 133 mL/min in healthy male volunteers. In the same volunteers, after a subcutaneous injection of 0.1 mg/kg ZOMACTON to the forearm, the mean peak serum concentration was 80 ± 50 ng/mL which occurred approximately 7 hours post injection and the apparent elimination half life was approximately 2.7 hours. Compared to intravenous administration, the extent of systemic availability from subcutaneous administration was approximately 70%.

Both strengths of ZOMACTON when administered by conventional subcutaneous injection and by the ZOMAJET needle-free device were compared in bioequivalence studies conducted in adults. Local tolerability of ZOMACTON administered via the ZOMAJET device was evaluated in an open safety study in children aged 3 to 17 years. Efficacy studies in the paediatric population comparing ZOMACTON administration via the ZOMAJET device and conventional needle injections have not been evaluated.

INDICATIONS
For the long-term treatment of children who have growth failure due to inadequate secretion of growth hormone.

CONTRAINDICATIONS
ZOMACTON should not be used in subjects with closed epiphyses.

ZOMACTON should not be used if there is evidence of an active tumour. Intracranial tumours should be inactive and anti-tumour therapy complete before initiating use of ZOMACTON (see PRECAUTIONS).

ZOMACTON should not be used in adults. No studies have been carried out to support its use in adults.

Multi-dose ZOMACTON vials, reconstituted with bacteriostatic saline, should not be used in patients with hypersensitivity to any of the excipients. ZOMACTON 4 mg must not be given to premature babies or neonates as the solvent contains benzyl alcohol (see PRECAUTIONS).

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure, or similar condition should not be treated with ZOMACTON.

PRECAUTIONS
Because of the diabetogenic effect of somatropin, ZOMACTON should be used with caution in patients with diabetes mellitus. Regular blood glucose testing and close supervision is imperative in such cases. Patients should be observed for evidence of glucose intolerance because growth hormone may induce a state of insulin resistance. ZOMACTON should be used with caution in patients with diabetes mellitus or with a family history predisposing for the disease. Strict monitoring of urine and blood glucose is necessary in these patients. In children with diabetes, the dose of insulin may need to be increased to maintain glucose control during ZOMACTON therapy.

Patients should be euthyroid before ZOMACTON treatment is initiated. Periodic monitoring of thyroid function is recommended to detect hypothyroidism emerging during treatment. During treatment with somatropin an enhanced T4 to T3 conversion has been found which may result in a reduction in serum T4 and an increase in serum T3 concentrations. In general, the peripheral thyroid hormone levels have remained within the reference ranges for healthy subjects. The effects of somatropin on thyroid hormone levels may be of clinical relevance in patients with subclinical hypothyroidism in whom hypothyroidism theoretically may develop. Conversely, in patients receiving replacement therapy with thyroxine mild

hyperthyroidism may occur. It is therefore particularly advisable to test thyroid function after starting treatment with somatropin and after dosage adjustments.

Patients with growth hormone deficiency secondary to intracranial lesions should be closely observed to detect progression or recurrence of the underlying disease. Discontinue ZOMACTON therapy if progression or recurrence of the lesion occurs (see CONTRAINDICATIONS).

Rare cases of benign intra-cranial hypertension have been reported. In the event of severe or recurring headache, visual problems, and nausea/vomiting, a fundoscopy for papilloedema is recommended. If papilloedema is confirmed, diagnosis of benign intra-cranial hypertension should be considered and if appropriate growth hormone treatment should be discontinued (see ADVERSE EFFECTS).

Steroid dosage greater than 15 mg/m^2 hydrocortisone or its equivalent may inhibit growth. Slipped epiphyses are more likely to occur in children receiving growth hormone, and any child with a limp should be evaluated as this may indicate a slipped epiphysis.

Local reaction at injection site should be avoided by changing the injection site to avoid the risk of lipoatrophy.

Although ZOMACTON is not indicated for use in patients who have Prader-Willi syndrome it should be noted that somatropin in contraindicated in patients with Prader-Willi Syndrome who are severely obese or have severe respiratory impairment.

Myositis is a very rare adverse event that may be related to the preservative meta-cresol in the diluent for ZOMACTON 10mg. In the case of myalgia or disproportionate pain at the injection site, myositis should be considered and, if confirmed, a ZOMACTON presentation without meta-cresol should be used.

Due to the presence of benzyl alcohol as an excipient in the diluent for ZOMACTON 4mg, toxic reactions and anaphylactoid reactions can occur in infants and children up to 3 years old (see CONTRAINDICATIONS).

In patients with previous malignant diseases special attention should be given to signs and symptoms of relapse.

Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during somatropin treatment.

Treatment with ZOMACTON should be discontinued at renal transplantation.

Effects on Fertility
Studies in animals have not been conducted to assess the effect of ZOMACTON on fertility.

Carcinogenicity
Associations between elevated serum IGF-1 concentrations and risks of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatropin who

do not have growth hormone deficiency and who are treated for prolonged periods, is not known.

Genotoxicity
Somatropin showed no evidence of mutagenic activity in bacterial or mammalian cells and showed no activity in an assay for DNA damage in rodent hepatic cells.

Use in Pregnancy (Category B2)
The use, safety and efficacy of ZOMACTON in pregnant women have not been established.

Use in Lactation
There have been no studies conducted with ZOMACTON in lactating women. It is not known whether this drug is excreted in human milk however, absorption of intact protein from the gastrointestinal tract of the infant is unlikely. Because many drugs are excreted in human milk, caution should be exercised when ZOMACTON is administered to lactating women.

Interactions with Other Medicines
Glucocorticoid therapy may inhibit the growth promoting effect of ZOMACTON. Patients with co-existing ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid impairment of the growth promoting effect of ZOMACTON.

High doses of androgens, oestrogens, or anabolic steroids can accelerate bone maturation and may, therefore, diminish gain in final height.

Because somatropin can induce a state of insulin resistance, insulin dose may have to be adjusted in diabetic patients receiving concomitant ZOMACTON.

Data from an interaction study performed on growth hormone deficient adults suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

ADVERSE EFFECTS
In clinical trials (n = 164) the following side effects were noted: headaches (14%), injection site pain (8%), injection site haematoma (4%), oedema (2%), hypothyroidism (6%). The incidence of side effects is similar to that seen in other growth hormone clinical studies.

The subcutaneous administration of growth hormone may lead to loss or increase of adipose tissue at the injection site. On rare occasions patients have developed pain and an itchy rash at the site of injection.

Somatropin has given rise to the formation of antibodies in approximately 1% of patients. The binding capacity of these antibodies has been low and no clinical changes have been associated with their formation.

Symptoms of fluid retention can be experienced, especially in the early phase of ZOMACTON therapy.

Rare cases of benign intra-cranial hypertension have been reported with somatropin (see PRECAUTIONS).

Leukaemia has been reported in a small number of patients treated with other growth hormone products. It is uncertain whether this risk is related to the pathology of growth hormone deficiency itself, growth hormone therapy, or other associated treatments such as radiation therapy for intracranial tumours.

	Common ≥1/100 and <1/10	Uncommon ≥1/1,000 and <1/100	Rare ≥1/10,000 and <1/1,000	Very rare <1/10,000
Neoplasms, benign and malignant				Leukaemia
Immune system disorders	Formation of antibodies			
Endocrine disorders	Hypoglycaemia		Diabetes mellitus type II	
Nervous system disorders		Carpal Tunnel Syndrome Paraesthesia	Transient headache Benign intracranial hypertension	
Musculoskeletal, connective tissue and bone disorders		Stiffness in the extremities, arthralgia, myalgia		
General disorders and administration site disorders	Injection site reaction	Peripheral oedema	Pain and itchy rash at injection site	Injection site fat atrophy or hypetrophy

DOSAGE AND ADMINISTRATION

ZOMACTON should be used only under the supervision of a qualified physician experienced in the management of patients with growth hormone deficiency. The subcutaneous administration of growth hormone may lead to loss or increase of adipose tissue at the injection site. Therefore, injection sites should be alternated.

ZOMACTON dosage must be individualised for each patient.

A dosage schedule of up to 0.1 mg/kg body weight administered three times weekly by subcutaneous injection is recommended.

As an alternative, a dose of 0.17 – 0.23 mg/kg bodyweight (approximately 4.9 mg/m^2 – 6.9 mg/m^2 body surface area) per week divided into 6 – 7 s.c. injections is recommended (corresponding to a daily injection of 0.02 – 0.03 mg/kg bodyweight or 0.07 – 1.0 mg/m^2 body surface area). The total weekly dose of 0.27 mg/kg or 8 mg/m^2 should not be exceeded (corresponding to daily injections of up to about 0.04 mg/kg).

After the dose has been determined, each vial is to be reconstituted only with the diluent supplied. The following volumes of diluent are recommended for reconstitution of ZOMACTON:

ZOMACTON 4 mg: to achieve a concentration of 3.3 mg/mL use 1.3 mL of diluent.
ZOMACTON 10 mg: to achieve a concentration of 10 mg/mL use entire contents of pre-filled diluent syringe.

To prepare the ZOMACTON, inject the diluent into the vial of ZOMACTON aiming the stream of liquid against the vial wall. Then swirl the product vial with a gentle rotary motion until the contents are completely dissolved. Do not shake.

After reconstitution, vial contents should be clear, without particulate matter. Occasionally, after refrigeration, some cloudiness may occur. This is not unusual for proteins like ZOMACTON. Allow the product to warm to room temperature. If the cloudiness persists or particulate matter is noted, the contents must not be used.

ZOMACTON may be administered using sterile disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy. Before and after injections, the septum of the vial should be wiped with alcohol to prevent contamination of the contents after repeated needle insertions.

Use with ZOMAJET device
ZOMACTON may also be administered by using the ZOMAJET needle free device. The ZOMAJET 2 Vision model is for use with ZOMACTON 4 mg and the ZOMAJET Vision X is for use with ZOMACTON 10 mg. Detailed instructions for use of the ZOMAJET are supplied with each device.

The ZOMAJET device is a needle free injection device designed to deliver growth hormone subcutaneously. There are three different sized heads, designated A, B and C which can be used with the device. Head A is appropriate for most patients; however, heads B or C may be required for a minority of patients to allow adequate administration of the somatropin.

The selection of the appropriate head is made when patients commence treatment. Patients are trained on the use of the device and to evaluate their injections in order to choose the optimal head. All patients initially begin using head A (smallest diameter). The injection is either complete ('dry') or incomplete ('wet') when used in accordance with the instructions. If the head is suitable, the injection will be 'dry'. If the injection is 'wet', they try head B and subsequently, if required, head C. Patients who still have problems with 'wet' injections using

the largest head (head C) are not good candidates for this type of administration. Once the optimal head is chosen, the patient continues with this head for all their injections, replacing the head after every 7 injections. This process ensures reproducible injections that do not impact on the systemic exposure of the growth hormone.

Detailed information on how to choose the optimal head is provided in the instructions for use supplied with the device. Once the optimal head is chosen and the correct administration technique is followed, the patient is confident that a complete ('dry') injection has resulted. The clinical data demonstrates bioequivalence of ZOMACTON administered via ZOMAJET (when used correctly and a 'dry' injection is achieved) and ZOMACTON administered via a conventional needle.

OVERDOSAGE

Long-term overdosage could result in some clinical features of acromegaly. Short-term overdosage may manifest as disturbances in glucose metabolism.

PRESENTATION

ZOMACTON 4 mg powder for injection vial with diluent vial (5mL); 1s
ZOMACTON 10 mg powder for injection vial with diluent prefilled syringe and adaptor (1 mL); 1s

Storage

ZOMACTON, before and after reconstitution, must be stored at 2 – 8ºC. Do not freeze. The reconstituted vials should be used within 14 days (4 mg) or 28 days (10 mg).

NAME AND ADDRESS OF SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
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Pymble NSW 2073

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine

Date of TGA approval: 3 September 2010