



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Australian Public Assessment Report for Rituximab

Proprietary Product Name: MabThera SC

Sponsor: Roche Products Pty Limited

**September 2014**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- 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.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

## About AusPARs

- 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 common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BSA	Body Surface Area
AUC	Area under concentration versus time curve
CI	Confidence Interval
CL	Clearance
CLL	Chronic Lymphocytic Leukaemia
C <sub>max</sub>	Maximum concentration
CMI	Consumer Medicines Information
CR	Complete Response
CRR	Complete Response Rate
CT	X-Ray Computed Tomography
C <sub>trough</sub>	Trough concentration
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ITT	Intention to Treat
IV	Intravenous
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin's Lymphoma
ORR	Overall Response Rate
PI	Product Information
PK	Pharmacokinetics
PP	Per Protocol

Abbreviation	Meaning
PR	Partial Response
rHuPH20	recombinant human hyaluronidase
SAE	Serious Adverse Event
SC	Subcutaneous
TGA	Therapeutic Goods Administration
T <sub>max</sub>	Time of maximum concentration
uCR	Unconfirmed Complete Response

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	New dose form, new strength, new route of administration, change in dosage.
<i>Decision:</i>	Approved
<i>Date of decision:</i>	26 May 2014
<i>Active ingredient:</i>	Rituximab
<i>Product name:</i>	MabThera SC
<i>Sponsor's name and address:</i>	Roche Products Pty Limited PO Box 255 Dee Why NSW 2099
<i>Dose form:</i>	Solution for injection
<i>Strength:</i>	1400mg/11.7mL
<i>Container:</i>	Glass vial
<i>Pack size:</i>	1 vial per pack
<i>Approved therapeutic use:</i>	<i>For treatment of patients with:</i> <ul style="list-style-type: none"><li>• <i>CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,</i></li><li>• <i>CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,</i></li><li>• <i>CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.</i></li></ul>
<i>Route of administration:</i>	Subcutaneous (SC)
<i>Dosage:</i>	Dependent on the condition of the patient. See Product Information (Attachment 1) for details.
<i>ARTG number:</i>	207334

## Product background

This AusPAR describes the application by the sponsor Roche Products Pty Ltd to add another presentation and route of administration for MabThera (rituximab [rch]). The new route of administration is via subcutaneous (SC) injection at a dose of 1400 mg regardless of body weight. The sponsor is proposing that this new formulation only be used for some of the already approved indications for MabThera; *the treatment of patients with non-Hodgkin's lymphoma.*

MabThera is currently approved for IV infusion, with dose dependent on body surface area (BSA), that is, 375 or 500 mg/m<sup>2</sup>. The proposed Product Information (PI) documents state that the first administration of MabThera should always be given by IV infusion. Subsequent doses can be administered via IV infusion or SC injection, with the appropriate formulation and dose.

Rituximab is a monoclonal antibody against CD20<sup>1</sup>. Rituximab is currently also indicated in chronic lymphocytic leukaemia, rheumatoid arthritis (RA), granulomatosis with polyangiitis and microscopic polyangiitis. In RA, a fixed dose is used.

The new presentation for SC use includes recombinant human hyaluronidase (also referred to as rHuPH20). The rHuPH20 is classified as a permeation enhancer and excipient. The amount of rHuPH20 in the SC formulation is 2,000 U per mL (or 23,400 U per dose), which is relatively high. This excipient is added to locally depolymerise the substrate hyaluronan (HA) at the site of injection in the subcutis, to allow the SC injection of high dose volumes to patients without pain or discomfort. See *Nonclinical findings*, *Pharmacology* below for more details on dermal repair.

### **Regulatory status**

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on the 21 August 1998. At the time the TGA considered this application, similar applications had been submitted to the European Union (EU), Switzerland and New Zealand. A positive CHMP opinion was received on January 23 2014 and marketing authorisation was authorised on 21 March 2014.

### **Product Information**

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

## **II. Quality findings**

### **Drug substance (active ingredient)**

The drug substance is identical to that used for the currently registered products, MabThera rituximab 100 mg/10 mL injection vial (AUST R 60318) and MabThera rituximab 500 mg/50 mL injection vial (AUST R 60319).

The active substance is a monoclonal antibody whose structure and biochemistry has been described previously.

Amino acid analysis data is consistent with the expected residues for the antibody. The complete amino acid sequence was confirmed through a number of analytical techniques.

The recombinant chimeric mouse/human monoclonal antibody rituximab was characterised to confirm the amino acid sequence and significant structural features.

Analysis of the oligosaccharides confirmed the expected glycosylation for an antibody produced in Chinese Hamster Ovary (CHO) cells.

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<sup>1</sup>CD20 is an activated-glycosylated phosphoprotein expressed on the surface of all B-cells beginning at the pro-B phase (CD45R+, CD117+) and progressively increasing in concentration until maturity. Its function is to enable optimal B-cell immune response, specifically against T-independent antigens



Only an abbreviated description of manufacture is presented here as the process has not changed since the original approval of MabThera except where indicated. Changes to the process and the rationale behind those changes are described. None of the changes pose a discernable risk to the safety or the quality of the product.

This substance is manufactured from cell supernatant taken from an antibody producing CHO cell line. Cell banking processes are satisfactory. All viral/prion safety issues have been addressed, including use of animal derived excipients, supplements in the fermentation process and in cell banking.

The production process for rituximab SC is identical to that for the approved rituximab v1.2 process with the exception of the ultrafiltration and diafiltration (UFDF) operations. The UFDF process was developed to produce rituximab SC at a 120 g/L concentration in the targeted formulation.

### Drug product

The proposed label name is MabThera rituximab (rch) 1400 mg/11.7 mL solution for injection presented in a glass Type 1 vial. MabThera drug product for subcutaneous injection is a sterile, colourless to yellowish, clear to opalescent solution supplied in 15 mL single use vials at 120 mg/mL, with an extractable volume of 11.7 mL (1400 mg/11.7ml).

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The product is not photo stable.

The proposed shelf life is 30 months when stored at 2°C to 8°C.

In-use stability data have also been submitted. The proposed shelf life and storage conditions for the opened/reconstituted/diluted product are 48 h when stored at 2°C to 8°C and subsequently 8 h at 30°C in diffuse sunlight.<sup>2</sup>

### Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological 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.

1. The novel excipient, recombinant hyaluronidase, does not have an International Nonproprietary Name (INN). The agreed interim name, 'hyaluronidase (human recombinant)', does not comply with TGO69<sup>3</sup>. While 'hyaluronidase' is an Australian Biological Name (ABN), the entry in the Ingredient database actually refers to extracts from mammalian tissues as defined in the European Pharmacopeia (EP)/British Pharmacopeia (BP) monograph for this substance. Also, there is no bio-descriptor. Adding a bio-descriptor to 'hyaluronidase' is technically inappropriate given the EP/BP definition.

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<sup>2</sup> Sponsor comment: Please note that these conditions were revised during the evaluation process. The approved PI has the following statement:

*"Once transferred from the vial into a syringe, the solution of MABTHERA SC formulation is physically and chemically stable for 48 hours at 2 – 8 °C and subsequently for 8 hours at 30 °C in diffuse daylight. However, as MABTHERA SC formulation does not contain any antimicrobial agent or preservative, use the product as soon as practicable after preparation to reduce microbiological hazard. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user. If storage is necessary, hold at 2 – 8 °C for not more than 24 hours."*

<sup>3</sup> TGO 69 is a standard for medicines made under section 10 of the Act. TGO 69 defines the applicable standards in Australia for the labelling of medicines.

The agreed name is only a temporary measure while waiting for approval of a proper INN. The sponsor has committed to applying for an INN prior to completion of the Category 1 evaluation and before registration can occur. A paragraph has been added to the letter to remind the sponsor of its commitments.

2. It is not clear whether all manufacturing and testing sites for rHuPH20 have TGA Good Manufacturing Practice (GMP) approval. An application from the sponsor is currently being processed by TGA.

These matters need to be resolved prior to registration.

The quality evaluator recommended that MabThera rituximab (rch) 1400 mg/11.7 mL solution for injection vial should be approved once issues around the nomenclature for the hyaluronidase excipient have been agreed and all the GMP clearances have been provided.<sup>4</sup>

### **Recommended conditions of registration**

#### ***Batch release testing by OLSS***

It is a condition of registration that, as a minimum, the first five independent batches of MabThera rituximab (rch) 1400 mg/11.7mL solution for injection vial imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

#### ***Certified product details***

An electronic draft of the Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>], should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

## **III. Nonclinical findings**

### **Introduction**

The nonclinical submission consisted of bridging studies to support the use of the SC formulation of rituximab and data to support the safety of the excipient, hyaluronidase. Overall, the data are appropriate to support the proposed new route of administration and new formulation.

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<sup>4</sup>Sponsor comment: These issues were resolved prior to approval of the product, that is,  
1) It was agreed that an interim name of "hyaluronidase (human recombinant)" for the excipient was acceptable.  
2) The manufacturing site for the excipient received TGA GMP clearance.

## Pharmacology

### Primary pharmacology

#### *Recombinant human hyaluronidase*

Recombinant human hyaluronidase is added to the formulation as a permeation enhancer. Hydrolysing hyaluronan, the principle glycosaminoglycan in the hypodermis, by hyaluronidase is expected to transiently reduce the viscosity of the 'gel-like' phase of the extracellular matrix, leading to increased hydraulic conductance that facilitates the dispersion and absorption of SC administered rituximab. This would allow patients to receive larger volumes by SC injection.<sup>5, 6</sup>

Pharmacology studies with hyaluronidase examined the effect on the dispersion area of a dye in the dermis of nude mice. An increase in the dye dispersion area was seen when hyaluronidase was administered intradermally at the same site or was provided intravenously. This increase in dye dispersion area was not seen when hyaluronidase was provided intradermally at a distal site. Systemic anti-hyaluronidase neutralising antibodies did not significantly inhibit intradermally administered hyaluronidase activity, although co injection of the antibodies with hyaluronidase inhibited the hydrolysing activity of the enzyme. The effect of systemic antibodies on the activity of SC injected hyaluronidase was not studied.

The action of hyaluronidase is rapid and dose/concentration dependent. With 2 units (U) of hyaluronidase, the majority of the hyaluronidase action occurred within 1 min. In mice, dermal repair was seen after 6 h post hyaluronidase (intradermal). Dermal repair in human subjects was shown to occur 24 to 48 h following hyaluronidase injection<sup>7</sup>, suggesting the interstitial layer should be fully repaired between weekly injections. The rapid repair is likely due to the typical rapid turnover of HA in the skin (15 to 20 h)<sup>8, 9</sup> and the short half-life of hyaluronidase activity in the skin (13 to 20 min in mouse skin).

No specific studies were submitted that assessed the ability to administer larger volumes via the SC route with the inclusion of hyaluronidase in the formulation. However, published data have indicated that the presence of hyaluronidase allows an increase in the SC infusion rate and administration of larger SC volumes, without swelling or tissue distortion.<sup>10</sup> Furthermore, the recombinant human hyaluronidase in the proposed SC formulation of rituximab is currently approved in the USA as an adjuvant to increase the dispersion and absorption of other injected drugs.

#### *Rituximab*

One pharmacology study compared the anti-tumour activity of the IV and SC formulations of rituximab in mice bearing SC xenografts of human NHL cells. SC doses higher than those used for IV administration, were required to provide equivalent tumour growth suppression.  $C_{\text{trough}}$  levels of rituximab from 5 mg/kg/week SC and 50 mg/kg/week SC were similar to those with 3 mg/kg/week IV and 30 mg/kg/week IV, respectively. In

<sup>5</sup> Frost, G.I. (2007) Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. *Expert Opin. Drug Deliv.* 4: 427–440.

<sup>6</sup> Kang, D.W., D.A. Oh, G.Y. Fu, J.M. Anderson and M.L. Zepeda. (2013) Porcine model to evaluate local tissue tolerability associated with subcutaneous delivery of protein. *J. Pharmacol. Toxicol. Methods* 67: 140–147.

<sup>7</sup> Bywaters, E.G.L., E.J. Holborow and M.K. Keech. (1951). Reconstitution of the dermal barrier to dye spread after hyaluronidase injection. *Br. Med. J.* 2: 1178–1183.

<sup>8</sup> Fraser, J.R. and T.C. Laurent. (1989) Turnover and metabolism of hyaluronan. *Ciba Found. Symp.* 143: 41–53.

<sup>9</sup> Laurent, U.B.G., L.B. Dahl and R.K. Reed. (1991) Catabolism of hyaluronan in rabbit skin takes place locally, in lymph nodes and liver. *Exp. Physiol.* 76: 695–703.

<sup>10</sup> Bookbinder, L.H., A. Hofer, M.F. Haller et al. (2006) A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J. Controlled Rel.* 114: 230–241.

general, similar  $C_{\text{trough}}$  levels are required following IV and SC administration to have similar anti-tumour efficacy.

A pharmacokinetic/pharmacodynamic study with the SC formulation of rituximab was conducted in Cynomolgus monkeys. As expected, based on the pharmacology of rituximab, there was a depletion of B cells. Both CD3<sup>-</sup>/CD20<sup>+</sup> and CD3<sup>-</sup>/CD40<sup>+</sup> B lymphocytes remained low while there were quantifiable serum levels of rituximab.

## Secondary pharmacodynamics and safety pharmacology

### *Recombinant human hyaluronidase*

No specific studies were submitted to assess possible secondary pharmacological effects of hyaluronidase. This is not considered a deficiency given the action of hyaluronidase is expected to remain local and the half-life of enzymatic activity in skin is relatively short and not associated with significant systemic exposure.

No specialised safety pharmacology studies with hyaluronidase were submitted. However, effects on the cardiovascular, respiratory and central nervous systems (CNS) were assessed in the pivotal 39 week repeat dose toxicity study with hyaluronidase in Cynomolgus monkeys. There were no clinical signs of CNS abnormalities or adverse effects on respiratory rate, blood pressure or electrocardiogram (ECG) waveforms in Cynomolgus monkeys that received  $\leq 2$  mg/kg/week SC hyaluronidase (170 times the clinical dose based on body surface area or 470 times the clinical dose based on mg/kg).

## Pharmacokinetics

### **Recombinant human hyaluronidase**

The plasma kinetics of hyaluronidase were examined in mice (single IV), Cynomolgus monkeys (single IV and SC, repeat SC) and human subjects (repeat SC dosing). The area under the plasma concentration time curve (AUC) increased more than dose proportionally in Cynomolgus monkeys that received IV doses of hyaluronidase. This pattern correlated with a dose related increase in the plasma half-life of hyaluronidase (5 to 91 min at 0.3 to 30 mg/kg) which may be a result of saturation of a clearance (or inactivation) mechanism. At similar IV doses (0.3 to 0.4 mg/kg), the elimination half-life was similar in mice and Cynomolgus monkeys (2.2 to 5 min). A published paper has indicated the plasma half-life of recombinant human hyaluronidase in rats following IV administration is also very short (<1 min at a dose of 0.075 mg/kg).<sup>5</sup> Following SC dosing to monkeys, peak plasma levels of hyaluronidase were seen 1 to 4 h postdose and the SC bioavailability was estimated to be low (2 to 5%). Absorption by the SC route was also demonstrated in pregnant mice and plasma levels increased with repeated dosing. In the clinical trials, only 1 out of 118 patients had quantifiable levels of hyaluronidase up to 1 h post dose (lower limit of quantification (LLOQ) 0.3125 U/mL), suggesting limited SC bioavailability and rapid clearance in patients. There was no evidence of accumulation following 7 daily SC doses to Cynomolgus monkeys. However, following SC dosing, exposures to hyaluronidase increased for up to approximately 3 months, after which the exposures began to decrease. The decrease in exposures correlated with the appearance of hyaluronidase neutralising activity (likely attributable to anti-hyaluronidase antibodies), probably enhancing clearance of the enzyme.

Consistent with other proteins, the volume of distribution of hyaluronidase was less than total body water in mice and monkeys suggesting that systemically, the enzyme is restricted to the vasculature. Following intradermal injection of 80 U, hyaluronidase activity could be detected in the skin near the site of injection for up to 1 h. The half-life in skin was estimated to be 13 to 20 min but there was no detectable systemic exposure.

Taken together, the data indicate the activity of the enzyme is transient and there is limited systemic exposure. Following IV administration to mice, enzyme activity was measured in plasma, liver, kidney and spleen.<sup>5</sup> The activity in all of these matrices was rapidly inactivated.

The metabolic fate and inactivation of hyaluronidase have not been elucidated. The presence and level of hyaluronidase was based on activity assays, rather than the entire enzyme. Hyaluronidase inhibitors are ubiquitous and potent, being present in virtually every mammalian tissue, including sera.<sup>11</sup> The chemical nature of the inhibitors is varied.<sup>11</sup> The presence of hyaluronidase inhibitors in most tissues is suggested to be critical to finely tune enzyme activity and enables rapid responses to situations of increased HA levels. Therefore, the pharmacokinetic findings of rapid inactivation of hyaluronidase activity in all tissues are not surprising. The inactivation of hyaluronidase is likely to be reversible. How well the profile of hyaluronidase activity in plasma mirrors the profile of total enzyme (active and inactive) is unclear.

### Rituximab

The serum kinetics of rituximab were monitored following IV and SC administration to mice and mini-pigs. The time to reach peak serum levels was significantly delayed following SC administration compared to IV administration with time to maximum plasma concentration ( $T_{max}$ ) values of 2 h in mice and 24 to 48 h in mini-pigs. The rate of absorption of rituximab was examined in mini-pigs with different hyaluronidase concentrations. In the presence of hyaluronidase, the rate of absorption of rituximab increased, with maximum plasma concentration ( $C_{max}$ ) values reached at 24 h compared to 48 h in the absence of hyaluronidase. This is consistent with previously published data indicating that hyaluronidase increases the  $C_{max}$  and decreases the time to  $C_{max}$  ( $T_{max}$ ) of co-administered proteins provided by SC injection.<sup>10</sup> This is suggested to be due to an increased dispersion area, increasing the surface area of local capillaries exposed to the injected drug, thereby increasing the rate by which the compound is absorbed.<sup>5</sup> Even in the presence of hyaluronidase, there is a significant delay in the time to peak serum levels of rituximab following SC administration (3 days SC compared to 1.5 h IV) in humans. This will need to be considered during clinical use.

The bioavailability of rituximab by the SC route was 52 to 71% in mice and mini-pigs and was independent of hyaluronidase concentrations in mini-pigs. Therefore, at least in this system, hyaluronidase had no significant effect on the bioavailability of rituximab provided by the SC route. Previous publications reported an increase in the SC bioavailability of protein drugs in the presence of hyaluronidase.<sup>10</sup> The difference between the published data and the study submitted here may be attributed to species differences (rats versus pigs) and associated differences in the SC tissue. Pigs are considered a better model. As an SC dose of 1400 mg is required to provide similar  $C_{trough}$  levels (concentration at the end of the dosage interval) (and by association, exposures) to that seen with an IV dose of 375 mg/m<sup>2</sup> (562.5 mg to a 50 kg individual), the estimated SC bioavailability in human subjects is approximately 50%<sup>12</sup>.

<sup>11</sup> Mio, K and R. Stern. (2002) Inhibitors of the hyaluronidases. *Matrix Biol.* 21: 31–37.

<sup>12</sup> The PI cites, based on population PK analysis, a human absolute bioavailability of 71%.

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## Toxicology

### Repeat-dose toxicity

Three repeat-dose toxicity studies in Cynomolgus monkeys were submitted; one assessing the toxicity of the SC formulation of rituximab and two assessing the toxicity of hyaluronidase (by the IV and SC routes).

#### *Rituximab*

The repeat-dose toxicity study with the SC formulation of rituximab was of 8 weeks duration and used the clinical (SC) formulation and one of the clinical dosage regimens (once/week). The duration of the study was acceptable, limited by the immunogenicity of rituximab in this species. The study design (dose and dosage regimen) was chosen to parallel the pivotal 8 week repeat-dose toxicity study that was submitted to support the IV formulation of rituximab (Study 54272). As noted in the original submission, the study had some limitations. Only a single dose was tested (20 mg/kg), resulting in subclinical exposures (exposure ratio based on AUC,  $[ER_{AUC}]$ , 0.2<sup>13</sup>). However, despite the low margin, there was almost complete depletion of B cells attained, demonstrating that a near maximum pharmacodynamic response had been achieved.

Aside from the expected reversible pharmacological effect of B cell depletion, no other systemic toxicities were noted in rituximab-treated monkeys. Injection site reactions (minimal acute inflammation with minimal necrosis) were seen in the majority of rituximab-treated animals (5/6) (see *Local tolerance*). As the systemic exposures (AUC) to rituximab appear to be higher (by approximately 1.3 times) with the SC formulation at the proposed clinical dose (1400 mg) compared to those seen with the currently approved IV dose (at 375 mg/m<sup>2</sup>), a higher incidence of toxicities or more severe toxicity may be seen with the new SC formulation of rituximab. This risk should be considered in conjunction with the potential benefits to patients.

#### *Recombinant human hyaluronidase*

The toxicity of hyaluronidase was assessed in Cynomolgus monkeys following 7 daily doses (at 5 mg/kg SC or IV) or 39 weekly doses (at  $\leq 2$  mg/kg SC). The duration of the studies is acceptable. The clinical route of administration and dosing regimen were used in the pivotal study. The chosen doses are acceptable, representing several times the clinical dose (Table 1).

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<sup>13</sup> Based on a combined male/female AUC of 23, 500  $\mu\text{g}\cdot\text{h}/\text{mL}$  in monkeys on day 1 of dosing, and a clinical AUC of 5320  $\mu\text{g}\cdot\text{day}/\text{mL}$ , or 127, 680  $\mu\text{g}\cdot\text{h}/\text{mL}$ .

**Table 1. Relative dose in the pivotal repeat-dose toxicity study with hyaluronidase**

Species	Study duration	Hyaluronidase dose			Dose ratio based on	
		mg/kg SC	kU/kg SC*	kU/m <sup>2</sup> #	kU/kg	kU/m <sup>2</sup>
Monkey (Cynomolgus)	39 weeks <i>Study 1017117</i>	0.02	2.2	26.4	5	1.7
		0.2	22	264	47	17
		2	220	2640	470	170
Human	–	–	23.4 kU (0.468 kU/kg)	15.6	–	–

\* based on the hyaluronidase activity of 110 kU/mg in the monkey study; # based on mg/kg to kU/m<sup>2</sup> conversions factor of 12 for monkeys, and assuming a human body surface area of 1.5 m<sup>2</sup> (50 kg individual)

No target organs for toxicity were identified in the repeat-dose toxicity studies with hyaluronidase. Some injection site reactions (minimal subcutaneous perivascular lymphoplasmacytic infiltration [plasma cells and lymphocytes]) were seen in animals given high SC doses ( $\geq 0.2$  mg/kg/week SC) of hyaluronidase. Otherwise, there were no clinically relevant toxicities identified with hyaluronidase.

### Genotoxicity and carcinogenicity

No studies assessing the genotoxic or carcinogenic potential of hyaluronidase were submitted. This is considered acceptable given the intended patient population and also that hyaluronidase is an endogenous protein.

### Reproductive toxicity

Submitted reproductive and developmental toxicity studies examined the effects of hyaluronidase on embryofetal development and pre/postnatal development in mice. The absence of a dedicated study examining effects on fertility is considered acceptable given the intended patient population and that effects on reproductive organs were assessed in the pivotal repeat-dose toxicity study. However, the IV formulation of rituximab is currently approved for use in patients with rheumatoid arthritis. Should the indications for the SC formulation of rituximab be extended from anticancer indications to other indications, a study assessing the effect of hyaluronidase (and anti-hyaluronidase antibodies) on fertility, should be submitted. While two species should normally be used in the assessment of effects on embryofetal development<sup>14</sup>, evidence of embryofetal lethality in mice with a plausible pharmacological explanation, provide sufficient evidence of risks to the developing embryo/fetus.

The pivotal studies were Good Laboratory Practice (GLP) compliant, used adequate animal numbers and dosing was performed in the appropriate gestational and postnatal periods. Adequate monitoring was included in the study design. Dosing was via the clinical route (SC) but with daily dosing (rather than weekly or monthly proposed clinically). Dosing daily is considered to be better than weekly dosing, given the critical time points during the organogenesis period. High relative doses were used in all studies (Table 2).

<sup>14</sup> ICH S5[R2]: Detection of toxicity to reproduction for medicinal products and toxicity to male fertility

**Table 2. Relative dose in the reproductive toxicity studies with hyaluronidase**

Species	Study	Hyaluronidase dose			Dose ratio based on	
		mg/kg SC	kU/kg	kU/m <sup>2</sup>	kU/kg	kU/m <sup>2</sup>
Mouse (CrI:CD 1[ICR])	Embryofetal development [Study 1034927]	3	357	1071	76 3	69
		9	1071	3213	22 88	20 6
		18	2142	6426	45 77	41 2
	Pre- /Postnatal development [Study 1034928]	3	360	1080	76 9	69
		6	720	2160	15 38	13 8
		9	1080	3240	23 08	20 8
Human	-	-	23.4 kU (0.468 kU/kg)	15.6	-	-

# based on mg/kg to mg/m<sup>2</sup> conversions factor of 3 for mice, and assuming a human body surface area of 1.5 m<sup>2</sup> (50 kg individual)

Following weekly dosing of ≤ 2 mg/kg/week SC hyaluronidase to male Cynomolgus monkeys, no abnormalities were detected during analyses of testicular volume, semen and hormones (testosterone and luteinizing hormone (LH)). In female monkeys, hyaluronidase had no effect on menstrual cycling. During postmortem analyses, no abnormalities were detected in the reproductive organs of either male or female monkeys. Therefore, adverse effects on fertility are not predicted based on available data with hyaluronidase.

Furthermore, hyaluronidase (PH20) is a sperm surface protein which plays a role in the binding of sperm to the egg zona pellucida<sup>15</sup> and has been shown to be essential for fertility in some species<sup>16,17</sup> but not others<sup>18</sup>. Therefore, direct adverse effects on fertility by SC administered hyaluronidase are unlikely. However, given the role of hyaluronidase (PH20) in fertilisation, antibodies against this enzyme have the potential to impair fertility. Guinea-pigs in which anti-PH20 antibodies were raised were infertile<sup>16</sup>. Infertility

<sup>15</sup> Lin, Y., L.H. Kimmel, D.G. Myles and P. Primakoff. (1993) Molecular cloning of the human and monkey sperm surface protein PH-20. *Proc. Natl. Acad. Sci. USA* **90**: 10071–10075.

<sup>16</sup> Primakoff, P., W. Lathrop, L. Woolman, A. Cowan and D. Myles. (1988) Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20. *Nature* **335**: 543–546.

<sup>17</sup> Pomering, M., R.C. Jones, M.K. Holland, A.E. Blake and K.W. Beagley. (2002) Restricted entry of IgG into male and female rabbit reproductive ducts following immunization with recombinant rabbit PH-20. *Am. J. Repro. Immunol.* **47**: 174–182.

<sup>18</sup> Hardy, C.M., G. Clydesdale, K.J. Mobbs, J. Pekin, M.L. Lloyd, C. Sweet, G.R. Shellam and M.A. Lawson. (2004) Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20. *Reproduction* **127**: 325–334.



in males was due to a loss of normal sperm in the epididymis<sup>19</sup>, while infertility in females was suggested to be due to prevention of sperm-egg binding by PH20 antibodies.<sup>16</sup> While anti-human hyaluronidase antibodies were raised in monkeys, with no apparent effect on sperm levels in males, no data were provided to demonstrate that the anti-human hyaluronidase antibodies in monkeys also bind to the PH20 orthologue in this species. Therefore, until further work is undertaken, no firm conclusions can be drawn from the lack of an effect on male reproductive parameters in the submitted toxicity studies. Despite having significant sequence similarity between the PH20 orthologues, antibodies raised against PH20 from a given species, do not always cross-react with PH20 from a different species (reviewed in Lin *et al.*, 1993<sup>15</sup>). It has been suggested that to test infertility, PH20 from that species must be used as an immunogen.<sup>15</sup> If the presence of anti-hyaluronidase antibodies in patients affects fertility, the infertility is likely to be long-lasting but would eventually be reversible. The potential effects on fertility are not considered a significant concern here for the current submission. The Product Information document already states that *Women of child-bearing potential must use effective contraceptive methods during treatment and for up to 12 months following MABTHERA® therapy.*

Embryofetal lethality was seen in mice treated with  $\geq 9$  mg/kg/day SC hyaluronidase. Reduced fetal weights were also seen at these doses. There was no evidence of teratogenicity at doses  $\leq 18$  mg/kg/day. The adverse embryofetal effects occurred in the absence of maternotoxicity, suggesting a direct test article related effect. The embryofetal lethality may be attributed to the pharmacological activity of hyaluronidase on the developing fetus. HA is the major glycosaminoglycan of the cardiac jelly, critical for the formation (and function) of the heart during embryogenesis. Deletion of hyaluronan synthase-2 in mice, leads to embryonic death<sup>20</sup>, similar to that seen with hyaluronidase, as HA appears to be essential for cardiac organogenesis. Systemic exposure was demonstrated in the mouse study with plasma  $C_{max}$  ranging from 3.4 to 50 U/mL on gestation day (GD) 6 (dosing Day 1) increasing to 21 to 99 U/mL on GD 15 (dosing Day 10) at 3 to 18 mg/kg/day (equivalent to 240 kU/kg/day), and  $AUC_{0-24h}$  5.45 to 120 U·h/mL on GD 15. As described above, very low plasma levels of hyaluronidase (generally below the LLOQ of 0.3125 U/mL) were reported in patients in clinical trials. Exposure at the No Observable Effect level (NOEL) (3 mg/kg/day SC) is estimated to be at least 69 times the proposed dose to be used clinically (based on dose per body surface area). Therefore, these findings are not expected to be relevant for the proposed clinical use.

There were no significant adverse effects on pup development in the pre/postnatal study in which mice were treated with  $\leq 9$  mg/kg/day SC hyaluronidase (at least 208 times the clinical dose [based on body surface area]). No studies have been conducted to assess the extent of excretion of hyaluronidase into milk.

### ***Pregnancy classification***

The current pregnancy category for MabThera is Category C<sup>21</sup>. Given the embryofetal deaths seen in mice can be attributed to the pharmacological activity of hyaluronidase, Pregnancy Category C is still considered appropriate for the SC formulation of MabThera.

<sup>19</sup> Tung, K.S.K., P. Primakoff, L. Woolman-Gamer and D.G. Myles. (1997) Mechanism of infertility in male guinea pigs immunised with sperm PH-20. *Biol. Reproduct.* **56**: 1133–1141.

<sup>20</sup> Camenisch, T.D., A.P. Spicer, T. Brehm-Gibson *et al.* (2000) Disruption of hyaluronan synthase-2 abrogates normal cardiac morphogenesis and hyaluronan-mediated transformation of epithelium to mesenchyme. *J. Clin. Invest.* **106**: 349–360.

<sup>21</sup> Australian Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

### ***Local tolerance***

The local irritation potential of the SC formulation of rituximab was assessed in rabbits. The clinical formulation was used but only a relatively small volume was injected subcutaneously (0.5 mL). There were no macroscopic or microscopic lesions that could be attributed to the test article. Reversible injection site reactions were seen in Cynomolgus monkeys that received SC formulations of rituximab (minimal acute inflammation with minimal necrosis) or high SC doses of hyaluronidase (minimal subcutaneous perivascular infiltration [plasma cells and lymphocytes]). These reactions are typical non-specific foreign body reactions. Nonetheless, injection site reactions may be seen during clinical use.

### **Immunogenicity**

#### ***Rituximab***

Anti-rituximab antibodies were detected in 6 out of 10 Cynomolgus monkeys that received weekly SC doses of rituximab (20 mg/kg). No adequate animal studies were conducted to compare whether anti-rituximab antibodies are more likely following SC dosing compared to IV dosing. Nonetheless antibody production in animals may not be predictive of the clinical situation.

#### ***Hyaluronidase***

Human hyaluronidase was immunogenic in Cynomolgus monkeys; all animals that received hyaluronidase in the pivotal 39 week repeat-dose toxicity study tested positive to anti-hyaluronidase antibodies, with most animals having neutralising activity. The only notable effect associated with antibody production was a decrease in systemic exposure to hyaluronidase. In mice, systemic neutralising antibodies had no effect on the activity of hyaluronidase in skin, suggesting anti-hyaluronidase antibody production in human subjects is not expected to affect the efficacy of hyaluronidase during SC administration. However, anti-hyaluronidase antibodies may have the potential to affect fertility in human subjects (see *Reproductive toxicity* above).

### **Nonclinical summary and conclusions**

The nonclinical data consisted of bridging studies to support the use of the SC formulation of rituximab and data to support the safety of the excipient, hyaluronidase. Overall, the data are appropriate to support the proposed new route of administration and new formulation.

#### **Rituximab**

- Compared with the IV formulation (and route), the formulation of rituximab (with hyaluronidase) when provided subcutaneously:
  - provided a similar anti-tumour efficacy profile in mice bearing NHL xenografts;
  - had a different pharmacokinetic profile with a delayed time to peak serum levels; this needs to be considered during clinical use;
  - at the maximum clinical dose, higher systemic exposure levels (AUC) were reported; this may indicate a higher risk for adverse events with this route of administration

## Hyaluronidase

- Pharmacology studies with hyaluronidase in mice demonstrated increased dermal dye dispersion. Pharmacokinetic studies indicated the enzyme activity was short lived (both locally and systemically) and there was limited SC bioavailability. Repeat-dose toxicity studies in Cynomolgus monkeys with high SC doses revealed no adverse effects. Embryofetal deaths and reduced fetal weights were seen in reproductive toxicity studies in mice. The no effect dose is estimated to be at least 69 times the proposed clinical dose.
- Treatment-related reactions were observed at the injection sites of Cynomolgus monkeys that received rituximab plus hyaluronidase. All reactions were reversible but the data suggest injection site reactions may be seen in the clinical setting.
- In treated Cynomolgus monkeys, antibodies were raised against both rituximab and hyaluronidase. The clinical relevance of these findings is unknown.

There are no objections on nonclinical grounds to the registration of MabThera solution for SC injection for the proposed indication.

The nonclinical evaluator recommended changes to the draft Product Information but the details of these are beyond the scope of this AusPAR.

## 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

#### Clinical rationale

According to the sponsor's Clinical Overview the conversion from IV to SC administration for other monoclonal antibodies '*... has resulted in shorter administration times, increased patient convenience, and improved cost-effectiveness, as well as an improved tolerability with fewer infusion-related reactions*'. The sponsor anticipated that similar benefits would be obtained with SC administration of rituximab.

#### Guidance

The following guidelines published by the European Medicines Agency (EMA) and adopted by the TGA are considered relevant to the current application:

- Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3.Corr)
- Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins (CHMP/EWP/89249/2004).

Compliance with these guidelines will be considered in the relevant sections of this report.

#### Contents of the clinical dossier

##### *Scope of the clinical dossier*

The submission contained the following clinical information:

- A clinical study report for one Phase Ib clinical trial (BP 22333 Stages 1 and 2) examining the pharmacokinetics, pharmacodynamics and safety of SC administration of rituximab in patients with follicular lymphoma;
- A clinical study report for one Phase III clinical trial (BO 22334 Stage 1) examining the pharmacokinetics, pharmacodynamics, efficacy and safety of SC administration of rituximab in patients with follicular lymphoma;
- 3 population pharmacokinetic analyses;
- Individual patient narratives (for patients who died, experienced a serious adverse event or experienced an adverse event that resulted in withdrawal) and summary safety data for subjects participating in an ongoing study of SC administration of rituximab for the treatment of CLL (BO 25341).
- Literature references.

### Paediatric data

The submission did not include paediatric data. As IV rituximab is not registered for use in children the absence of such data is not considered a major deficiency.

### Good clinical practice

The study reports for the three submitted clinical trials included assurances that they were conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidelines and any regulations applicable in the countries where the trials were conducted. Study protocols, consent forms etc. were reviewed by independent ethics committees.

### Pharmacokinetics

#### Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic topic.

**Table 3. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID	*
PK in NHL patients	General PK - Dose finding	BP 22333 Stage 1	*
	- Dose confirmation	BP 22333 Stage 2	*
		BO 22334 Stage 1	*

\* Indicates the primary aim of the study

#### **Study BP 22333 stage 1**

Examined the PK of various SC dosing regimens (given on a mg/m<sup>2</sup> of body surface area [BSA] basis) with the objective of identifying one that would produce comparable serum concentrations (C<sub>trough</sub>, AUC) to those seen with conventional IV dosing. Using the data generated, a population PK analysis was then conducted to determine a suitable fixed dose (that is, one not based on BSA).

**Study BP 22333 stage 2**

Directly compared the fixed SC dose (determined in BP 22333 Stage 1) with the conventional IV dose. The data generated were analysed using another population PK analysis.

**Study BO 22334 stage 1**

Also directly compared PK parameters following the proposed SC and conventional IV dosing.

A population PK analysis was then conducted on all PK data collected in BP 22333 Stages 1 and 2 and BO 22334 Stage 1. The analysis was used to determine covariates that affected rituximab PK and to predict rituximab PK in various situations.

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

**Summary of pharmacokinetics**

The submitted studies demonstrated the following:

- A fixed SC dose of 1400 mg produced non-inferior  $C_{\text{trough}}$  levels compared to the conventional IV dose of 375 mg/m<sup>2</sup> IV;
- The 1400 mg SC dose also resulted in an increased total systemic exposure (AUC) compared to the conventional IV dose of 375 mg/m<sup>2</sup> IV. The increase in AUC was in the range of 35 to 43%.
- BSA affects the pharmacokinetics of rituximab. In patients receiving a fixed SC dose of 1400 mg systemic exposure will be greater in subjects with lower BSA.
- The absolute bioavailability of rituximab after SC administration is approximately 70%.
- Systemic absorption of the novel excipient rHuPH20 was undetectable in most patients.

**Evaluator's conclusions on pharmacokinetics**

The proposed dosage regimen of 1400 mg SC has been demonstrated to produce systemic concentrations of rituximab that are not inferior to those produced by IV administration of 375 mg/m<sup>2</sup>. The sponsor's argument that this dose should therefore be associated with comparable efficacy is acceptable.

However, the proposed SC dosing regimen is associated with a significant increase in overall systemic exposure to the drug and this is more marked in subjects with low BSA. It might reasonably be expected that the SC dosage regimen will be associated with increased toxicity compared to the current IV dosage regimen.

**Pharmacodynamics****Studies providing pharmacodynamic data**

In both the submitted studies the peripheral blood CD19+ lymphocyte count was monitored. CD19 is a marker of B-lymphocytes.

***CD 19 +ve lymphocyte count***

In BP 22333 Stages 1 and 2, all patients had already received rituximab as part of induction treatment as well as at least one dose as part of maintenance treatment. Subjects therefore had depletion of CD19+ve lymphocytes with median counts = 0 at baseline.

In BP 22333 Stage 1, available data from patients at a 9 month follow-up visit showed some increase in B-cell levels at this time point compared with previous time points, with median counts of 50 (Cohort A, n = 6), 30 (Cohort B, n = 16), 20 (Cohort C, n = 15) and 30 cells/mm<sup>3</sup> (Cohort D, n = 7).

In BP 22333 Stage 2, CD19+ve lymphocyte counts remained depleted throughout treatment with evidence of recovery in the small number of patients who had completed their 9 month follow up visit.

In BO 22334 Stage 1, CD19+ve cells were depleted soon after commencement of rituximab therapy in both treatment arms. Levels remained depleted throughout induction and early maintenance treatment.

**Dosage selection for the pivotal studies**

The proposed dosage regimen for SC use (a fixed dose of 1400 mg for all patients) was justified on pharmacokinetic criteria. Study BP 22333 demonstrated that this regimen would produce trough serum concentrations of rituximab that were non-inferior to those produced by the standard IV dose of 375 mg/m<sup>2</sup>.

**Efficacy****Studies providing efficacy data*****Pivotal efficacy data***

Only one of the two submitted studies (BO 22334 Stage 1) contained clinical efficacy data.

Comment: As described below, examination of efficacy was a secondary objective in BO 22334 Stage 1 and no formal efficacy hypothesis was tested. It might therefore not be considered a 'pivotal' efficacy study. However, as it provides the only clinical efficacy data in the submission, it will be considered pivotal for the purposes of this review.

Study BO 22334 is a two stage study. The primary objective of Stage 1 was a pharmacokinetic one, that is, to estimate the ratio of serum trough concentrations obtained with SC and IV administration. The primary objective of Stage 2 will be of efficacy, that is, to estimate the overall response rates obtained with SC and IV administration. The design of Stages 1 and 2 was identical except that Stage 1 involved more intensive pharmacokinetic sampling. The submission only contained data from Stage 1 of the study.

**Evaluator's conclusions on efficacy**

The clinical data suggest that subcutaneous and intravenous administration produce similar efficacy. However, no formal efficacy hypothesis was tested in the submitted study and hence these data should be considered supportive. The main evidence to support comparable clinical efficacy is the pharmacokinetic data described above (and in Attachment 2).

## Safety

### Studies providing evaluable safety data

#### *Studies in NHL patients*

The following studies conducted in NHL patients (described above) provided evaluable safety data:

- Study BP 22333 Stage 1. Subjects received a single dose of 375 mg/m<sup>2</sup> IV, 375 mg/m<sup>2</sup> SC, 625 mg/m<sup>2</sup> SC or 800 mg/m<sup>2</sup> SC as part of maintenance treatment;
- Study BP 22333 Stage 2. Subjects received ongoing treatment with either 375 mg/m<sup>2</sup> IV or 1400 mg SC as part of maintenance treatment.
- Study BO 22334 Stage 1. Subjects received ongoing treatment with either 375 mg/m<sup>2</sup> IV or 1400 mg SC as part of both induction and maintenance treatment.

For the type of safety data collected, please see Attachment 2.

#### *Study in CLL patients*

Study BO 25341 (the SAWYER study) is an ongoing, two part, randomised, open label, parallel group, multicenter, Phase Ib study in patients with previously untreated chronic lymphocytic leukaemia (CLL).

## Patient exposure

### Safety issues with the potential for major regulatory impact

#### *Liver toxicity*

Laboratory testing of liver function in the submitted studies did not demonstrate any evidence of hepatic toxicity with SC dosing.

#### *Haematological toxicity*

Rituximab is given in conjunction with cytotoxic chemotherapy during induction treatment for NHL and hence haematological toxicity is not uncommon. Study BO 22334 Stage 1 raises the possibility of increased haematological toxicity with SC administration and this is discussed further below.

#### *Serious skin reactions*

Cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported with rituximab and these events are listed in the product information. No cases were reported in the studies included in this submission.

#### *Cardiovascular safety*

The currently approved product information for rituximab notes that cardiovascular AEs have been associated with the drug (hypotension, angina, cardiac arrhythmias). The safety data submitted with the current application did not suggest an increased risk of these events with SC administration.

#### *Unwanted immunological events*

Antibodies to rituximab or rHuPH20 developed in a small proportion of patients. These did not appear to be associated with adverse outcomes.

**Postmarketing data**

There were no postmarketing data included in the submission.

**Evaluator's conclusions on safety**

In both of the randomised, repeated dose studies the SC regimen/product was associated with some increase in toxicity compared to the IV regimen.

- Although the proportion of patients who developed AEs was comparable with SC and IV administration, the total number of AEs was increased with the SC route (291 versus 257 events and 528 versus 363 events). The additional AEs were mainly administration related events (ARRs), that is, events that occurred in the first 24 h and were considered to be related by the investigators. Typically these consisted of injection site events (such as erythema and pain) and skin events (for example erythema). ARR were typically Grade 1 or 2 in severity.
- The proportion of subjects who developed Grade 3+ AEs was comparable with SC and IV administration in both studies. However, in BO 22334 Stage 1, where rituximab was administered in conjunction with chemotherapy during induction, the total number of Grade 3+ AEs was increased with SC administration (72 versus 41 events). As shown in Attachment 2, there was a suggestion of increased Grade 3+ haematological toxicity with SC administration.
- The proportion of patients who developed serious AEs (SAEs) was comparable with SC and IV administration in both studies. However the total number of SAEs was increased with SC administration in BO 22334 Stage 1 (33 versus 21 events), with an increased occurrence of febrile neutropaenia (10 versus 3 events).
- SC administration was not associated with an increased incidence of fatal AEs or AEs leading to discontinuation.
- Apart from the possibility of increased haematological toxicity suggested by Study BO22334 Stage 1, there was no evidence from laboratory testing (biochemistry, urinalysis, vital signs, electrocardiogram (ECG), left ventricular ejection fraction (LVEF) testing etc.) of increased toxicity with SC administration.
- Antibodies to rituximab or rHuPH20 developed in a small proportion of patients. However, these did not appear to be associated with adverse outcomes. There did not appear to be an increased incidence of anti-rituximab antibodies with SC administration.

Based on the submitted clinical data, it is not possible to determine whether any of the toxicity observed with the SC route is due to the novel excipient rHuPH20.

**First round benefit-risk assessment****First round assessment of benefits**

The benefits of subcutaneous administration of rituximab in NHL patients are:

- A degree of efficacy comparable to that seen with IV administration;
- Increased convenience for patients, with the SC injection being given over 5 to 6 minutes, compared to an IV infusion given over a number of h (375 mg/m<sup>2</sup> IV given at rates between 100 and 400 mg per hour).
- In maintenance therapy, where rituximab is given as monotherapy, no intravenous access would be required.



**First round assessment of risks**

The risks of subcutaneous administration of rituximab in NHL patients are:

- Some increase in toxicity, mainly due to injection site events and skin events occurring in the first 24 h. These events were typically mild to moderate in severity (Grades 1 and 2).
- A possible increase in Grade 3 or higher/serious haematological events when rituximab is given in conjunction with chemotherapy during induction treatment.

Comment: This assessment of risks is based on a limited safety database. Of the 303 subjects treated with SC rituximab, 123 received only one cycle of treatment. No patient received a full (2 year) course of maintenance treatment.

It should be noted that the sponsor is collecting additional safety and efficacy data in Study BO 22334 Stage 2, where an additional 280 subjects will be randomised to SC or IV administration. The study will collect data during both induction and maintenance treatment.

As detailed in the 'Adverse effects' section of the current PI for IV rituximab, the drug has previously been associated with an increased incidence of Grade 3 and 4 leukopaenia and neutropaenia when given in combination with chemotherapy, compared to chemotherapy alone.

**First round assessment of benefit-risk balance**

The benefits of SC administration over IV administration are limited to patient convenience, with no demonstrated efficacy advantage.

These benefits come at a cost of some increase in toxicity in terms of administration-related reactions. Also, one of the submitted studies suggests that there may be some exacerbation of chemotherapy induced myelosuppression associated with the SC route. The increased myelosuppression may be a manifestation of the greater systemic rituximab exposure obtained with SC administration compared to IV administration. Previous studies in NHL and CLL have shown that IV rituximab in combination with chemotherapy is associated with an increased incidence of Grade 3 and 4 leukopaenia and neutropaenia compared with chemotherapy alone. In these studies, the additional toxicity produced by rituximab was outweighed by an efficacy benefit. No efficacy benefit has been demonstrated for SC rituximab over IV rituximab.

The safety database is also limited, especially in relation to long-term administration.

In the opinion of the clinical evaluator, an assessment of the risk-benefit balance of SC rituximab should be delayed until additional safety data are available from BO 22334 Stage 2. These additional data may clarify the issue of possible increased haematological toxicity and would provide additional evidence for safety during long term maintenance treatment.

On the available evidence it is not possible to conclude that SC administration of rituximab has a favourable risk-benefit balance.

**First round recommendation regarding authorisation**

It is recommended that the current application be rejected.

## Clinical questions

### Efficacy and safety

Please advise when the results of Study BO 22334 Stage 2 will be available.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan, EU RMP Version 9.1 dated 1 November 2012 with Australian Specific Annex Version 2.0 dated 13 March 2013 which was reviewed by the TGA's Office of Product Review (OPR).

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

**Table 4. Ongoing safety concerns**

Important Identified Risks	<ul style="list-style-type: none"> <li>• Acute Infusion-Related Reactions*</li> <li>• Infections*</li> <li>• Impaired Immunisation Response*</li> <li>• PML*</li> <li>• Neutropenia (including prolonged)*</li> <li>• HBV Reactivation*</li> <li>• Tumour Lysis**</li> <li>• Serious Viral Infections**</li> <li>• GI Perforation**</li> <li>• PRES**</li> <li>• Hypogammaglobulinaemia***</li> </ul>
Important Potential Risks	<ul style="list-style-type: none"> <li>• De Novo HBV***</li> <li>• Opportunistic Infections*</li> <li>• Malignant Events***</li> <li>• Impact on Cardiovascular Disease***</li> <li>• GI Perforation ***</li> <li>• Prolonged B-cell depletion**</li> <li>• Grade 3/4 and serious blood and lymphatic system AEs in &gt;70year patients**</li> <li>• AML/MDS**</li> <li>• Second malignancies**</li> <li>• off label use in autoimmune disease***</li> <li>• off label use in paediatric patients*</li> <li>• Embryofoetal toxicity resulting from systemic exposure to rHuPH20 (rituximab SC)*</li> </ul>
Important Missing Information	<ul style="list-style-type: none"> <li>• Use in Pregnancy and Lactation*</li> <li>• Immunogenicity and Autoimmune Disease***</li> <li>• Immunogenicity associated with the subcutaneous formulation</li> </ul>

\* All indications

\*\* NHL/CLL

\*\*\* RA and GPA/MPA

The sponsor proposes routine pharmacovigilance activities to monitor the specified ongoing safety concerns which pertain to the proposed subcutaneous dosage variation, namely “Embryofoetal toxicity” and “Immunogenicity associated with the SC formulation”. Additional pharmacovigilance appears to be proposed for the risk “Immunogenicity associated with the SC formulation”.

The sponsor concludes that routine risk minimisation activities are sufficient for all ongoing safety concerns, except in the case of “*embryofoetal toxicity resulting from systemic exposure to rHuPH20 (rituximab SC)*”, where additional risk minimisation is proposed.

The sponsor has submitted an EU RMP Version 9.1 dated 1 November 2012 with Australian Specific Annex Version 2.0 dated 13 March 2013. The reasoning for the

sponsor's change from the previously approved Core RMP v2.0 to an EU RMP v8 were addressed in reference to a previous submission: *"the sponsor identified differences between these documents in the Milestone 4 Response to Section 31 Questions (dated 2 November 2012). The sponsor committed to updating the Australian RMP to address these discrepancies. The submission of this EU RMP with the ASA fulfils each of those commitments."*

The sponsor provides the following summary of changes:

*"Version 9.0 of the EU RMP was updated from EU RMP v8.0 in response to EU assessment reports of previous RMP versions and also assessment of the GPA/MPA indication extension dossier. The changes were as follows;*

- *the addition of "off label use in autoimmune disease" and "off label use in paediatric patients" as potential risks*
- *addition/updating epidemiological data for each risk*
- *neutropenia moved from potential to identified risk (no additional risk minimisation actions)*
- *Addition of description of RAVELOS (the long term extension study for the RAVE GPA/MPA study)*
- *The potential risk of prolonged B cell depletion is now for all indications, not just NHL/CLL (no additional risk minimisation actions)*
- *Addition of updated (September 2011) RA all exposure clinical trial data"*

*Changes from EU RMP v9.0 to v9.1*

- *updates related to the introduction of the SC formulation*
- *new potential risk of embryofetal toxicity with the SC formulation based on pre-clinical data*
- *immunogenicity associated with the SC formulation added as important missing information*
- *potential and/or identified risks that could be associated with off label use of the SC formulation and medication error (primarily administration route error) are discussed in sections 1.9.5 Off label use in Haemato-oncology, and 3.2 Potential for Medication Error."*

*"Changes from ASA v1.0 to ASA v2.0*

- *updates related to the introduction of the subcutaneous (SC) formulation*
- *updates to reflect change in reference prescribing information from the company Core Data Sheet (CDS) to EU Summary of Product Characteristics (SPC)*
- *updates to reflect change in reference RMP (Core RMP to EU RMP, see below)"*

### **Reconciliation of issues outlined in the RMP report**

The following is a summary of the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

#### **1. Recommendation by OPR evaluator**

It is recommended that the following be added to the list of ongoing safety concerns:

1. Hepatobiliary events:
2. Medication error/Administration route error:

### 3. Off label use of the SC formulation:

#### *Sponsor's response*

The sponsor agrees to add 'Administration route error' and 'Off label use of the SC formulation' to the list of ongoing safety concerns when the RMP is next updated.

The evaluator's request to add 'Hepatobiliary events' to the list of ongoing safety concerns may be based on the reasonable assumption that because there is a guided questionnaire (GQ) entitled 'Hepatobiliary events', that hepatobiliary events per se are a special safety concern for MabThera. However, the sponsor would like to clarify that the GQ entitled 'Hepatobiliary events' is intended only for cases involving suspected hepatitis B reactivation (see response to RMP Recommendation 4). Hepatobiliary events in general have never been considered a potential or identified risk for MabThera and there is currently no concern of any relationship between MabThera and such events other than those involving hepatitis B reactivation. Hepatitis B reactivation is clearly an identified risk for MabThera, and is described in detail in the RMP.

#### **2. Recommendation by OPR evaluator**

The sponsor makes the following statement in regards to the pharmacovigilance plan for the ongoing safety concern of 'Immunogenicity associated with the SC formulation': *'Regular assessment of anti-rituximab and anti-rHuPH20 antibodies will continue in ongoing and planned studies involving the SC formulation.'* (EU RMP v9.1 table 120). However, the sponsor does not specify to which studies they are referring. Table 116 in the EU-RMP v9.1 lists only one planned study. This is BA28478 (Drug utilisation Study) PASS, with listed milestone as 'To be submitted to EMA for review'. It is recommended that the sponsor specify the protocols of the 'ongoing and planned studies involving the SC formulation'.

#### *Sponsor's response*

Immunogenicity data have been collected in patients in the SC studies submitted to support the MabThera SC formulation application (BP22333, BO22334 and BO25341), all of which were ongoing at the time of the application. Study BP22333 has subsequently been completed, whereas Studies BO22334 and BO25341 are still ongoing. Details of these studies including estimated timelines are provided below. Details of these studies will be provided when the RMP is next updated.

Actions	Milestones/Exposure	Estimated milestones/Calendar	Study Status
BO25341	170 patients	CSR 2015	Ongoing
BO22334	530 patients	Data included in version 9.1 of the EU RMP	Ongoing
BP22333	140 patients	Data included in version 9.1 of the EU RMP	Completed

Sponsor correction: 'The exposure value for BO22334 is a typographical error. "530 patients" should read "410 patients.'

#### **3. Recommendation by OPR evaluator**

The guided questionnaire regarding Hepatitis B should be submitted to the TGA for review.

#### *Sponsor's response*

With their response, the sponsor provided a draft update to the guided questionnaire (GQ) used for cases involving hepatitis B reactivation, updated with fields to capture information on route of administration. It should be noted that the title of the GQ is 'Hepatobiliary events'.

However, the GQ is not used to collect information on cases involving hepatobiliary events generally but only for cases involving suspected hepatitis B reactivation. The GQ was based on an existing document with the title 'Hepatobiliary events', and modified

accordingly, but the original title was maintained. Additional fields to capture information concerning route of administration have been added to this version of the GQ. The additional text is still in draft form but will be finalised before supply of the SC formulation. The additional text will be similar for all existing MabThera GQs.

#### **4. Recommendation by OPR evaluator**

The sponsor states that *'All current guided questionnaires for rituximab (PML, PRES, Malignancy, Pediatric Use) will be updated to capture information on route of administration and indication'*. It is recommended that the sponsor confirm that the questionnaires regarding hepatobiliary events and hepatitis B will also be updated and also provide assurance that all questionnaire's will be updated prior to supply of the SC formulation of rituximab.

##### *Sponsor's response*

The sponsor confirms that all existing guided questionnaires (GQs) will be updated with fields to capture route of administration and indication, including the GQ used for cases involving suspected hepatitis B reactivation, prior to supply of the SC formulation.

Please note that the GQ entitled 'Hepatobiliary events' is used to capture information only in patients with suspected hepatitis B reactivation (see responses to RMP Recommendations 2 and 4). This GQ should also have been mentioned along with the other GQs (PML, PRES, Malignancy and Pediatric Use) in the statement provided in the RMP. The omission will be corrected when the RMP is next updated.

#### **5. Recommendation by OPR evaluator**

It is recommended that the sponsor submit a copy of the proposed Australian educational materials to the TGA for review prior to marketing approval.

##### *Sponsor's response*

The sponsor submitted the EU specific educational material 'Administration Guide' and 'Comparison Card' which were first submitted in the EU in September as part of the ongoing evaluation of the subcutaneous MabThera formulation line extension application.

These educational materials will be adapted for Australia by replacing EU specific information with Australia specific information once the TGA evaluation has concluded and the Australian registration details are finalised. For example, the following information will likely require adaption to the local registered details.

- Administration Guide
  - Indications
  - Excipient naming
  - Labelling
  - Details on the method of administration
- Comparison Card
  - Labelling

The sponsor also proposes to consult with healthcare professionals (physicians, pharmacists and nurses) in a series of meetings in 2013 to gather feedback on the local applicability of the EU specific educational materials. The feedback from healthcare professionals will be used to amend the materials, if required.

In line with a revised proposal in the ongoing evaluation of the subcutaneous MabThera formulation in the EU, educational material for healthcare providers is no longer proposed as an additional risk minimisation activity in the context of embryofetal toxicity resulting

from systemic exposure to rHuPH20 but is now proposed in the context of administration-route error and off label use of the SC formulation. The activity was originally proposed within the context of systemic exposure to rHuPH20 on the understanding that administration route error (that is, accidental IV administration of the SC formulation) would be a prerequisite for systemic exposure to rHuPH20. However, after further consideration and discussions with Health Authorities, the sponsor considers that this activity is more logically addressed in the context of administration-route error itself.

The same material will emphasise the approved indications for the MabThera SC formulation, and is therefore also considered an 'additional' risk minimisation activity concerning off label use of the SC formulation.

#### **6. Recommendation by OPR evaluator**

The sponsor proposes to measure the effectiveness of this educational material through '*passive HCP feedback*'. This does not appear adequate as a method to assess the effectiveness of these materials. It is recommended that the sponsor actively investigate the effectiveness of these materials, or further define and justify the process of '*passive HCP feedback*'. The sponsor also refers to an 'effectiveness survey' regarding the educational material. It is recommended that a copy be submitted to the TGA for review when the educational materials are submitted.

#### *Sponsor's response*

The sponsor has reviewed and reconsidered the most appropriate methods for measuring the effectiveness of the educational material since the original application was submitted.

At present, the sponsor proposes to assess effectiveness of the education material using both process and outcome indicators. Distribution of educational material to healthcare providers will be considered as a process measure (details provided below).

The incidence of administration route errors involving the SC formulation will be assessed from reports of adverse events involving administration route errors and will be used as an outcome indicator, although this measure is likely to underestimate the true incidence of such errors, given that not all errors lead to adverse events. Similarly, the incidence of adverse events associated with off label use of the SC formulation will be used as an indicator of the extent of off label use, although is likely to underestimate the true incidence of off label use. The extent to which inappropriate off label use can be reduced by healthcare provider education is uncertain, given that off label use is often intentional. Therefore, a high incidence of adverse events associated with off label use, from which the sponsor may infer a high incidence of off label use per se, may not necessarily indicate a lack of knowledge.

The sponsor proposes to distribute the finalised educational materials via a direct mail-out following TGA registration but prior to supply. The following healthcare professionals (HCPs) will be included: haematologists, oncologists, rheumatologists, immunologists, hospital pharmacists and nurse unit managers. A mail out of the educational materials to the target groups will be repeated at the time of Pharmaceutical Benefits Scheme (PBS) listing. The list of individuals on the distribution list who were sent the materials will be retained. The distribution will be monitored by recording any returned correspondence indicating the mailed materials were not received. The concept of surveying HCPs directly to assess knowledge or behaviour is attractive. However, such surveys should be used with caution, as these capture only self-reported data and participation itself may induce behaviour changes. In addition, responses are more likely to be obtained from motivated, engaged HCPs and therefore may not represent the intended target audience [reference to *Guideline on good pharmacovigilance practices (GVP) Module XVI*]. Specific items/questions in a survey of this type are also difficult to design in such a way that the information obtained is valid and interpretable. Furthermore, direct surveys place an

additional burden on HCPs which in the context of these specific safety concerns is not likely to be justifiable given the value of the information obtained. Given this background, the sponsor considers that the effectiveness measures proposed in this response are appropriate.

#### **7. Recommendation by OPR evaluator**

It appears that section 1.9.1 of the EU RMP does not contain recent data and has not been updated regarding the SC formulation. The sponsor should update this information accordingly.

##### *Sponsor's response*

The sponsor commits to amending the RMP as requested when it is next updated.

#### **8. Recommendation by OPR evaluator**

The OPR evaluator recommended amendments to the draft PI in regards to the proposed Routine risk minimization activities, Overdosage and Use in Pregnancy sections but the details of these are beyond the scope of this AusPAR.

##### *Sponsor's response*

The sponsor acknowledges the RMP evaluator's recommendations for the PI. Based on the evaluator's recommendation that the PI and CMI should not be revised until the Delegate's Overview has been received, the PI and CMI have not been amended based on these recommendations. The sponsor will wait to review any requested PI changes included in the Delegate's Overview.

#### **9. Recommendation by OPR evaluator**

Safety Communication released on the 26 September 2013 regarding a new boxed warning with recommendations to decrease the risk of Hepatitis B reactivation, the wording within the Australian PI should be strengthened to the effect of:

- All patients should be screened for HBV infection before starting treatment with rituximab by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).
- Consult with hepatitis experts regarding monitoring and use of HBV antiviral therapy when screening identifies patients at risk of HBV reactivation due to evidence of prior HBV infection.
- Monitor patients with evidence of prior HBV infection for clinical and laboratory signs of hepatitis B or HBV reactivation during rituximab therapy and for several months following completion of therapy with these drugs.
- In patients who develop reactivation of HBV while on rituximab, immediately discontinue the drug and start appropriate treatment for HBV. Also discontinue any chemotherapy the patient is receiving until the HBV infection is controlled or resolved. Because of insufficient data, no recommendation can be made regarding the resumption of rituximab in patients who develop HBV reactivation hepatitis.

##### *Sponsor's response*

The sponsor acknowledges the RMP evaluator's recommendations for the PI. Based on the evaluator's recommendation that the PI and CMI should not be revised until the Delegate's Overview has been received, the PI and CMI have not been amended based on these recommendations. The sponsor will wait to review any requested PI changes included in the Delegate's Overview.

However, the sponsor would like to make the following comments:

In reference to the recommendation regarding Hepatitis B:

The sponsor highlights to the OPR evaluator a recent Safety Related Request application for the PI which focused on strengthening the precautionary information and recommendations regarding Hepatitis B. This submission was submitted to TGA on 5 August 2013 following consultation with OPR and approved on 24 September 2013.

The changed text regarding Hepatitis B is now included in the current version of the PI published on the TGA eBS website (see *Precautions, Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia, Infections and Precautions, Rheumatoid Arthritis (RA), Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA), Infections*).

These changes have not been integrated into the draft IV and SC formulation PIs provided with these responses. However, the sponsor intends to provide consolidated drafts of IV and SC formulation PIs in the pre ACPM response document that include all texts approved subsequent to the submission of the application for MabThera SC formulation in March 2013.

#### **10. Recommendation by OPR evaluator**

In regards to the proposed routine risk minimization activities, the Delegate may wish to revise the draft consumer medicine information document to reflect the approved changes to the Product Information.

##### *Sponsor's response*

Based on the RMP evaluator's recommendation that the PI and CMI should not be revised until the Delegate's Overview has been received, the CMI has not been amended at this stage of the evaluation.

#### **Summary of recommendations**

It was considered that the sponsor's response has adequately addressed all of the issues identified in the RMP evaluation report. However, two outstanding issues should be noted (see below).

#### **Outstanding issues**

##### *Issues in relation to the RMP*

- A number of routine risk minimisation measures are suggested by the RMP evaluator in regards to the Australian Product Information. The sponsor will consider these with the Delegate's Overview.
- The sponsor should submit the updated Australian education materials to the TGA for review prior to market approval.

#### **Suggested wording for conditions of registration**

##### *RMP*

Implement EU RMP Version 9.1 dated 1 November 2012 with Australian Specific Annex Version 2.0 dated 13 March 2013.

## **VI. Overall conclusion and risk/benefit assessment**

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



## Quality

The quality evaluator identifies two issues:

1. naming of the novel excipient (recombinant hyaluronidase)
2. GMP status of the product.

The sponsor has applied for an International Nonproprietary Name; the agreed interim name is 'hyaluronidase (human recombinant)'. The evaluator states that an approved Australian Approved Name (AAN) is required irrespective of the INN application.<sup>22</sup>

GMP status for manufacturing and testing sites for rHuPH20 was questioned by the quality evaluator. In the sponsor's response, the sponsor notes that only GMP clearance for the primary manufacturer of rHuPH20 has been sought. In the EU, in the case of SC Herceptin, 'it was acceptable that Roche was responsible to ensure the manufacturer is in compliance with current GMP'.

Otherwise, no objections were raised to registration.

A proposed condition of registration (batch release conditions) was recommended.

## Nonclinical

There was no nonclinical objection to registration.

The nonclinical evaluator noted:

*No specific studies were submitted to assess possible secondary pharmacological effects of hyaluronidase. This is not considered a deficiency, given the action of hyaluronidase is expected to remain local and the half-life of enzymatic activity in skin is relatively short and not associated with significant systemic exposure.*

The nonclinical evaluator raised issues relating to fertility and embryofetal lethality:

*The absence of a dedicated study examining effects on fertility is considered acceptable given the intended patient population and that effects on reproductive organs were assessed in the pivotal repeat-dose toxicity study. However, the IV formulation of rituximab is currently approved for use in patients with rheumatoid arthritis. Should the indications for the SC formulation of rituximab be extended from anticancer indications to other indications, a study assessing the effect of hyaluronidase (and anti-hyaluronidase antibodies) on fertility, should be submitted. ...given the role of hyaluronidase (PH20) in fertilisation, antibodies against this enzyme, have the potential to impair **fertility**...*

***Embryofetal lethality** was seen in mice treated with  $\geq 9$  mg/kg/day SC hyaluronidase. Reduced fetal weights were also seen at these doses. There was no evidence of teratogenicity at doses  $\leq 18$  mg/kg/day. The adverse embryofetal effects occurred in the absence of maternotoxicity, suggesting a direct test article-related effect. The embryofetal lethality may be attributed to the pharmacological activity of hyaluronidase on the developing fetus. HA is the major glycosaminoglycan of the cardiac jelly, critical for the formation (and function) of the heart during embryogenesis.*

*As described above, very low plasma levels of hyaluronidase (generally below the LLOQ of 0.3125 U/mL) were reported in patients in clinical trials. Exposure at the NOEL (3 mg/kg/day SC) is estimated to be at least 69 times the proposed dose to be*

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<sup>22</sup>At the time of this AusPAR, hyaluronidase was considered an acceptable interim name for this excipient until an internationally agreed name is approved.

*used clinically (based on dose per body surface area). Therefore, these findings are not expected to be relevant for the proposed clinical use.*

The sponsor reported one spontaneous abortion in a 40 year old woman in Study BP22333 receiving 1400 mg SC rituximab.

## Clinical

The clinical evaluator recommends rejection of the application. Note however that the sponsor's responses to the clinical evaluation have been taken into account in this Delegate's Overview. A second round Clinical Evaluation Report was not generated.

## Overview of data

Supportive clinical data were from:

### **Study BP22333, 'SparkThera'**

This was a Phase Ib trial of pharmacokinetic (PK), pharmacodynamic (PD) and safety of SC rituximab in follicular lymphoma:

- Stage 1: SC dose-finding
- Stage 2: use of a SC 1400 mg dose versus IV dosing in a **maintenance** setting

### **Study B022334, 'SABRINA'**

This was a Phase III trial of PK, PD, efficacy and safety of SC rituximab in follicular lymphoma:

- Stage 1: SC 1400 mg dose versus IV dosing, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, vincristine, and prednisone (CVP) as part of **induction** treatment of (previously untreated) follicular NHL.<sup>23</sup>
- Stage 2: ongoing study of outcomes at end of induction phase and use in maintenance; results not analysed here.

## **Other**

- 3 population PK studies
- Some safety data from Study B025341, 'SAWYER', an ongoing study of SC rituximab in CLL (a complete study report was not provided).

## Formulation

The formulation used in the submitted clinical trials was the same as that proposed for registration in Australia.

A comparison of the excipients contained in the IV and SC formulations was provided.

The volume of solution required to deliver the proposed SC dose of 1400 mg is 11.7 mL (in contrast, a typical SC bolus injection of other medicines may be 1-2 mL).

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<sup>23</sup> Both Stages 1 and 2 of SABRINA had the same study design (apart from a more intensive PK sampling schedule in Stage 1). Therefore both Stages evaluated MabThera SC in the induction and maintenance phases of treatment.

## Pharmacokinetics (PK)

The sponsor's approach to comparison of SC and IV formulations is to establish that the SC formulation produces a non-inferior degree of target site saturation with rituximab, as implied by achieving serum  $C_{trough}$  and AUC with SC rituximab 'at least as high' as those after IV administration.

SC dose-finding Study BP22333 Stage 1 is detailed in the CER (See Attachment 2). The study aimed to find a SC dose yielding comparable  $C_{trough}$  and AUC to IV dosing. Participants had follicular NHL and had achieved an objective response following induction therapy that included at least 4 cycles of IV rituximab.

Based on outcomes of Study BP22333 Stage 1, a population PK approach was used to find a fixed SC dose that would produce non-inferior  $C_{trough}$  values compared to IV dosing at 375 mg/m<sup>2</sup>. This resulted in a 1400 mg SC dose being tested in Stage 2 versus IV 375 mg/m<sup>2</sup> dosing. A revised population PK model, taking into account PK data from Study BP22333 Stages 1 and 2 (and data from 298 NHL patients in previous trials) was used to predict PK outcomes at Cycle 2 of maintenance, after induction with 8 cycles every three weeks (q3wk). It was predicted  $C_{trough}$  would be higher with 1400 mg SC than with 375 mg/m<sup>2</sup> IV, for dosing both every 2 months (q2m) and every 3 months (q3m); predicted AUC was also higher, by approximately 35%.

Study B022334 Stage 1 then compared serum concentrations of rituximab at Cycle 7 of induction treatment (SC versus IV dosing).  $C_{trough}$  was again not lower with SC dosing (approximately 62% higher), while AUC was also higher by approximately 38%. The increased exposure with SC dosing was most pronounced in patients with low body surface area (subgrouping by BSA) and in females.

A population PK analysis of data from Studies BP22333 and B022334 broadly confirmed the above results and found a trend towards increased exposure with lower body surface area.

## Pharmacodynamics (PD)

Monitoring of CD19+ B cells in a limited number of patients did not provide influential PD data in support of (or against) the application.

## Efficacy

The clinical evaluator accepts the sponsor's argument that 'non-inferior' exposure to rituximab should translate into comparable efficacy.

Study B022334 Stage 1 included efficacy outcomes as a *secondary* objective (PK results, the primary focus of the study, have been referred to above). B022334 Stage 2 focuses on efficacy (and includes additional efficacy endpoints); the submission did not include data from that stage of the study.

Stage 1 is discussed in the CER (Attachment 2). Objective response rates (ORRs) were compared across study arms (SC versus IV rituximab), in induction treatment of previously untreated follicular lymphoma. Rituximab was given with CHOP or CVP. In the first cycle, *all* patients received IV rituximab but in subsequent induction cycles rituximab was given IV or SC according to randomisation. Maintenance doses were IV or SC as per induction usage.

The clinical evaluator accepted use of ORR and complete response (CR) at the end of induction phase as efficacy endpoints.

Sixty-four subjects were randomised to IV rituximab and 63 to SC rituximab. There were more females in the SC arm (59%) than the IV arm (48%) and this was reflected in

differing mean weights (71.9 kg versus 74.8 kg) and to a lesser extent the mean BSAs (1.80 versus 1.84 m<sup>2</sup>).

ORR at end of induction was 90.5% (SC arm) versus 84.4% (IV arm); the difference was not statistically significant. Complete response rates were 46% and 29.7% respectively (again not statistically significant, p=0.058). There was an indication of relatively high exposure to rituximab with SC dosing in patients with low BSA but this did not translate (in subgroup analysis of BO22334 Stage 1) to higher ORR with SC rituximab in patients with low BSA. If anything, patients with high BSA had better outcomes in the SC arm than in the IV arm.

### Safety

The clinical evaluator is concerned that higher exposure to rituximab with SC dosing may translate into more toxicity.

### Exposure

A total of 303 subjects were assessed for safety after receiving SC rituximab; 123/303 received only 1 cycle.

In Study BO25341 in CLL patients received up to 1870 mg rituximab SC.

The clinical evaluator focused on those studies lending themselves to direct comparison of the safety of SC and IV rituximab (BP22333 Stage 2 and BO22334 Stage 1).

### General comments

An overview of safety is provided below.

**Table 6. Overview of safety data for MabThera**

	BP22333, Stage 2 (MAINTENANCE) <sup>a</sup>		BO22334, Stage 1 (INDUCTION) <sup>b</sup>	
	Rituximab IV 375 mg/m <sup>2</sup> N=77 No. (%)	Rituximab SC 1400 mg N=77 No. (%)	Rituximab IV 375 mg/m <sup>2</sup> + Chemo N=65 No. (%)	Rituximab SC 1400 mg + Chemo N=62 No. (%)
Total patients with at least one:				
AE	61 (79)	61 (79)	57 (88)	57 (92)
<i>total number of AEs</i>	257	291	363	528
Grade ≥3 AE	13 (17)	14 (18)	30 (46)	29 (47)
Serious AE	11 (14)	9 (12)	14 (22)	14 (23)
ARR	3 (4)	24 (31)	21 (32)	31 (50)
AE leading to withdrawal	4 (5)	4 (5)	3 (5)	2 (3)
AE leading to death	0 (0)	0 (0)	0 (0)	1 (2)
Deaths	0 (0)	1 (1)	0 (0)	1 (2)

Several differences in safety profile of IV and SC rituximab are suggested by results in this summary table. First, the total number of AEs was higher in SC than in IV cohorts. Second, administration related reactions (ARRs) were more prominent in SC cohorts.

Another general comment is that the scatter of individual AEs across arms was not even (for example, BP22333 Stage 2; cough; nasopharyngitis; rash; urinary tract infection (UTI)). This may be a product of the relatively small number of subjects under study.

### Proportion of subjects with AEs versus total number of AEs

A higher number of AEs in SC cohorts (despite similar patient numbers across cohorts) was seen for the following categories of event: AEs; Grade 3+ AEs (in BO22334 Stage 1); and serious AEs (in BO22334 Stage 1).

The sponsor argues that *'inferences concerning the comparative safety of the SC and IV formulations should be based primarily on the proportion of patients who experienced one or more events, rather than on the total number of events in each cohort'*.

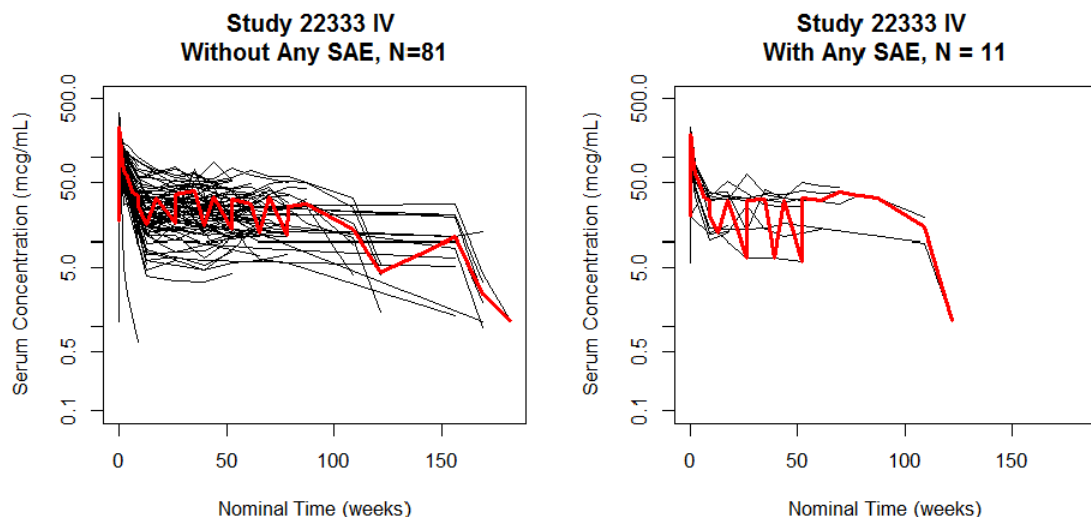
The Delegate agrees that analysis of the proportion of patients with AEs should be the primary approach but if a difference is also observed in the number of events per cohort, this should be taken into account.

In this setting where for example in B022334 Stage 1 Grade 3+ AEs were reported in 46% (IV) versus 47% (SC), the Delegate considers it informative that there were 41 such AEs across 30 patients in the IV cohort versus 72 such AEs across 29 patients in the SC cohort. This suggests patients experiencing Grade 3+ AEs had to manage a greater burden of AEs in the SC cohort.

The sponsor considers such findings as derived post hoc from multiple pairwise comparisons among a large number of outcome variables and raises concern about false-positive findings. Given the plausibility of the finding (via increased exposure), the onus is on the sponsor to exclude the possibility of a real effect for example via generation of further data (such as Stage 2 of B022334). The reviewed studies enrolled too few subjects to rule out a real increase in clinically significant AEs with the 1400 mg SC formulation.

The sponsor argues that occurrence of SAEs, Grade 3+ AEs and ARRs were not associated with rituximab exposure during maintenance monotherapy. A representative analysis in support of this view is shown below.

**Figure 3. Patients with and without any SAEs tabulated against serum plasma concentration and time of exposure.**



It is accepted that one patient in the SC cohort (#1286) with multiple AEs may have skewed results to some extent.

#### ***Administration related reactions***

These were defined differently across studies but in essence were '*reactions or adverse events that the investigator considered related to rituximab and which occurred within 24 h of administration*'.

Across all studies, ARRs were more frequent with SC than with IV administration. The sponsor states they were primarily injection site reactions such as pain, swelling and redness and were generally Grade 1 or 2 in severity and transient.

In BP22333 Stage 2, the commonest ARR was 'erythema' (13% of SC patients); also common were 'injection site erythema' (5% of SC patients), myalgia (5% of SC patients), pain (4% of SC patients) and swelling (4% of SC patients).

In B022334 Stage 1, common ARRs were injection site erythema (10% in the SC cohort), erythema (8%), pruritus (6%) and rash (6%). One patient had a Grade 3 injection site rash after the first SC injection at Cycle 2.

The sponsor describes the imbalance regarding ARRs as '*a change that is not medically relevant to the overall safety profile of rituximab*'. In the Delegate's opinion, local tolerability is an aspect of the overall safety profile and should be taken into account.

### **Neutropenia**

There was a higher incidence of neutropenia with SC than with IV administration.

In BP22333 Stage 2 (maintenance use), neutropenia was reported in 6% (SC) versus 3% (IV).

In BO22334 Stage 1 (induction use, in combination with chemotherapy), neutropenia was reported in 35% (SC) versus 35% (IV). Febrile neutropenia was reported in 10% (SC) versus 3% (IV). Treatment-related neutropenia was reported in 23% (SC) versus 9% (IV).

The sponsor's response for further information notes that with regard to BO22334 Stage 1:

*Neutropenia and/or febrile neutropenia were reported in 24/65 patients (37%) in the IV cohort and 26/62 patients (42%) in the SC cohort throughout the study period including Cycle 1 (rituximab given IV in all patients).*

*At Cycle 1, when all patients received rituximab intravenously, neutropenia/febrile neutropenia was reported in 11/62 patients (18%) in the SC cohort and 6/65 patients (9%) in the IV cohort. Over Cycles 2-8, neutropenia/febrile neutropenia was reported in 24/62 patients (39%) in the SC cohort and 21/64 patients (33%) in the IV cohort.*

*The greater incidence reported after Cycle 1 when all patients received rituximab intravenously suggests that baseline differences and/or differences in reporting may have contributed to at least some of the apparent difference between each treatment cohort at Cycles 2-8.*

*Of the 17 patients (6 patients IV vs 11 patients SC) who experienced neutropenia/febrile neutropenia at Cycle 1, 3/6 patients (50%) in the IV cohort and 9/11 patients (82%) in the SC cohort experienced neutropenia/febrile neutropenia during Cycles 2-8. Of the 110 patients (59 patients IV vs 51 patients SC) who did not experience neutropenia/febrile neutropenia at Cycle 1, 18/59 patients (31%) in the IV cohort and 15/51 patients (29%) in the SC cohort experienced neutropenia/febrile neutropenia at one or more subsequent cycles.*

Some baseline differences or difference in reporting may have impacted on outcomes but this situation detracts from the study's ability to answer whether there is a genuine difference in neutropenia with SC use of rituximab.

It is unclear whether studies could detect any real difference in frequency of late onset neutropenia between IV and SC rituximab arms, given median time to onset is reported to be up to 175 days<sup>24</sup>. Late-onset neutropenia is not commonly associated with clinical sequelae.

Oncologists are highly experienced in managing neutropenia and febrile neutropenia but it remains important to know how much more neutropenia can be expected with SC use relative to IV use of rituximab.

### **Other**

There was a 4% incidence of pneumonitis with SC rituximab in BP22333 Stage 2 (0% for IV rituximab) (of the 3 cases: 2 were considered treatment related; and 2 were in patients

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<sup>24</sup> Dunleavy K et al. Rituximab-associated neutropenia. *Semin Haematol* April 2010; 47: 180-186

with low BSA). Rituximab can cause pulmonary toxicity<sup>25</sup> and the current studies do not rule out a higher rate of this AE with SC use of a 1400 mg fixed dose. It is concerning that there were 2 reports of treatment related pneumonitis out of 77 patients in the SC arm of BP22333 Stage 2. Onset was not early in any case (onset dates were 162, 284 and 348 days after first drug administration).

SC administration of a therapeutic protein may be considered more immunogenic but there was no clear difference in development of anti-rituximab antibodies across patients given IV and SC rituximab.

### **Clinical evaluator's recommendation**

The clinical evaluator recommended that the current application be rejected.

### **Risk management plan**

The RMP proposed by the sponsor was considered generally acceptable by the TGA's Office of Product Review.

The RMP Evaluator recommends the following condition of approval:

- Implement EU RMP Version 9.1 dated 1 November 2012 with Australian Specific Annex Version 2.0 dated 13 March 2013

### **Risk-benefit analysis**

#### **Delegate's considerations**

##### ***Convenience***

Better convenience would support approval but evidence is lacking. Would the need for IV cannulation be avoided? The PI for IV MabThera recommends use of a dedicated line and administration prior to chemotherapy suggesting the SC route may spare the patient IV cannulation; on the other hand, hospital staff may prefer to have an IV line in place even when using SC rituximab (given warnings in the PI about hypersensitivity).

Administration time would fall significantly, although EviQ does note the use of off label rapid rituximab infusion<sup>26</sup> after safe completion of a first dose, reducing infusion time to 60 to 90 minutes. The advantage of reduced administration time is offset by the need for a protracted, possibly painful SC injection. Patients would avoid the need for prolonged IV infusion but given the altered PK of the SC administration of the agent, hospital staff may prefer to monitor patients for some time after SC rituximab (the PI recommends 'at least 15 minutes' noting that a longer period may be appropriate for patients with an increased risk of hypersensitivity; but the EU Summary of Product Characteristics (SmPC) for SC Herceptin recommends at least 2 h of monitoring).

*Delegate's question for ACPM:*

*Please advise about how much more convenient this SC use would be for the patient and/or clinician and how this should be weighed vs efficacy and safety factors.*

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<sup>25</sup> Liote H et al. Rituximab-induced lung disease: a systematic literature review. *European Respiratory J* 2010; 35 (3): 681-687

<sup>26</sup> <<https://www.eviq.org.au/AdditionalClinicalInformation/tabid/64/id/44/Default.aspx?popup=1>>

### Local tolerability

Improvement in tolerability is not particularly evident for SC rituximab: administration related reactions were much common with SC than with IV rituximab and the studies were too small to detect any difference in frequency of major infusion-related reactions.

### Safety and efficacy

The sponsor's aim was to find a fixed dose that resulted in a non-inferior trough concentration of rituximab (relative to IV dosing in NHL). This aim was achieved, but exposure appears higher with SC dosing than with IV. Whether this improves efficacy is not known, despite hints in the literature of dose-response correlations<sup>27</sup>; the studies reviewed here cannot answer that question. The sponsor has not argued for an efficacy benefit with the SC approach.

There are various protocols for treatment of NHL that include rituximab + chemotherapy, other than rituximab + CHOP or rituximab + CVP. A view of EviQ NHL protocols is included as Table 7 below. There is no formal evidence in support of use of this formulation/route of administration in those other settings but bridging from the SABRINA study where CHOP or CVP was used seems reasonable in that regard.

**Table 7. EviQ NHL protocols**

Burkitt Lymphoma dmCODOX-M/IVAC Treatment Overview
Burkitt Lymphoma Dose Modified CODOX-M (CYCLOPHOSPHamide DOXOrubicin Methotrexate)
Burkitt Lymphoma IVAC (IFOSFamide Etoposide Cytarabine)
Mantle Cell Lymphoma R-maxi-CHOP and R-HiDAC Treatment Overview
Non-Hodgkin Lymphoma Chlorambucil and RITUXimab
Non-Hodgkin Lymphoma CHOP14 (CYCLOPHOSPHamide DOXOrubicin vinCRISTine Prednisolone)
Non-Hodgkin Lymphoma CHOP21 (CYCLOPHOSPHamide DOXOrubicin vinCRISTine Prednisolone)
Non-Hodgkin Lymphoma DA-R-EPOCH (Dose Adjusted RITUXimab Etoposide Prednisolone vinCRISTine CYCLOPHOSPHamide DOXOrubicin)
Non-Hodgkin Lymphoma DHAC (Dexamethasone Cytarabine cARBOplatin)
Non-Hodgkin Lymphoma ESHAP (Etoposide Methylprednisolone Cytarabine cISplatin)
Non-Hodgkin Lymphoma Hyper CVAD Part A and B/POMP treatment Overview
Non-Hodgkin Lymphoma ICE (IFOSFamide cARBOplatin Etoposide)
Non-Hodgkin Lymphoma R-CHOP14 (RITUXimab CYCLOPHOSPHamide DOXOrubicin vinCRISTine Prednisolone)
Non-Hodgkin Lymphoma R-CHOP21 (RITUXimab CYCLOPHOSPHamide DOXOrubicin vinCRISTine Prednisolone)
Non-Hodgkin Lymphoma R-CVP (RITUXimab CYCLOPHOSPHamide vinCRISTine Prednisolone)
Non-Hodgkin Lymphoma R-DHAP (RITUXimab Dexamethasone Cytarabine cISplatin)
Non-Hodgkin Lymphoma RICE (RITUXimab Fractionated IFOSFamide cARBOplatin Etoposide)
Non-Hodgkin Lymphoma RITUXimab
Non-Hodgkin Lymphoma RITUXimab Maintenance
Primary CNS Lymphoma (PCNSL) (Methotrexate and Cytarabine)
Primary CNS Lymphoma (PCNSL) High Dose Methotrexate
Primary CNS Lymphoma (PCNSL) MBVP (Methotrexate Carmustine Teniposide Prednisolone)

Does increased exposure translate to worse toxicity? The evaluator's main concern in this regard was that one of the two studies suggested more neutropenia. The sponsor cast doubt on this interpretation by analysing the incidence of neutropenia in Cycle 1 (where both arms received IV rituximab) and by analysing a relationship between AEs and exposure (and not finding any striking relationship). Despite this, due to the small sample size of the pivotal studies some concern remains about whether the increase in exposure with SC rituximab translates to a worse systemic toxicity profile. For example, there was an imbalance in reports of pneumonitis.

*Delegate's questions for ACPM:*

*Please consider the data in support of this application and advise the Delegate about whether there is sufficient evidence of efficacy and safety to support registration of this product and route of administration.*

<sup>27</sup> Cartron G et al. Interindividual variability of response to rituximab: from biological origins to individualised therapies. Clin Cancer Res 2011; 17: 19-30



*If the evidence is considered by the ACPM insufficient to support registration (or sufficient only to support registration in some way differing from that requested by the sponsor), please explain this position.*

### **Summary of issues**

- Bridging of information about IV use to the SC setting, based on pharmacokinetic comparison of IV and SC use.
- Evidence for differing safety profile (SC versus IV)

### **Proposed action**

The Delegate was not in a position to say, at this time, that the 1400 mg rituximab product for SC use should be registered. The advice of the Committee was requested (see *Request for ACPM advice* below).

### **Request for ACPM advice**

Request from the Advisory Committee on Prescription Medicines (ACPM) was requested on the following points:

- Please consider the data in support of this application and advise the Delegate about whether there is sufficient evidence of efficacy and safety to support registration of this product and route of administration.
- If the evidence is considered by the ACPM insufficient to support registration (or sufficient only to support registration in some way differing from that requested by the sponsor), please provide reason/s.
- Please advise about how much more convenient this SC use would be for the patient and/or clinician and how this factor should be weighed versus efficacy and safety factors.
- Please advise the Delegate of any additional concerns or issues raised by this application, for example with regard to practical usage issues, Product Information, Consumer Medicine Information and so on.

### **Response from sponsor**

#### ***Comment on the delegate's proposed action***

The Delegate was not in a position to say that the MabThera subcutaneous (SC) product should be registered.

The sponsor considers that the MabThera (rituximab) SC formulation has a favourable benefit risk profile, comparable to that of the registered intravenous (IV) formulation and is expected to increase clinician and patient convenience and healthcare resource utilisation.

The sponsor considers that the current data support its proposal for registration in non-Hodgkin's lymphoma (NHL) indications of the current IV formulation.

#### ***Comment on the delegate's overview***

##### *Convenience and advantages of the SC formulation*

To date, MabThera is approved in over 120 countries globally and is the current standard of care for patients with NHL. The marketed formulation of MabThera is for IV administration where the dose is generally given over 2.5 to 4 h. A formulation of

MabThera has been developed for SC administration as an alternative to the currently marketed IV administration which is expected to lead to significant advantages for patients as well as healthcare providers in terms of comfort and convenience that may result in improved treatment compliance. Presented as a fixed dose formulation, the MabThera SC injection can be prepared and administered within minutes, thereby potentially contributing to the alleviation of resource constraints and reducing costs associated with IV administration. Distinct benefits are anticipated when the product is used in the monotherapy setting (no concurrent IV chemotherapy) but benefits are also expected during combination therapy.

Patients should be observed for at least 15 minutes following MabThera SC administration and although a longer period may be appropriate in patients with an increased risk of hypersensitivity reactions, the patient monitoring following SC administration as well as the total time including administration and monitoring will be significantly lower compared to IV administration.

A survey of oncology practitioners<sup>28</sup> showed that most considered SC administration to be more cost effective than IV infusion in terms of resource utilisation<sup>29</sup>, suggesting that MabThera SC will have a better cost-effectiveness profile than MabThera IV. Furthermore, SC administration was considered to result in higher patient satisfaction than IV administration<sup>29</sup> and it therefore considered that the SC administration has the potential to improve patient quality of life.<sup>30</sup>

The Time and Motion study, a multinational, multi center, prospective, observational study conducted alongside the MABCUTE (MO25455; NCT01461928) trial, collected data for MabThera SC injections and compared them with real life MabThera IV infusions in 23 centres.<sup>31</sup> The final results reported at the American Society of Hematology (ASH) in 2013 indicates that a switch from MabThera IV to MabThera SC leads to a substantial reduction in administration chair time (ranging from 64% to 86% depending on the country) and in active healthcare providers time (ranging from 27% to 57% depending on the country). These time savings could allow more time to be used for other patient care activities, increasing the number of patients who could be treated and thus increasing the overall efficiency of treatment centres. This is aligned with national and state health priorities to effectively manage increasing demand for health services through adoption of medical and technological innovation.<sup>32,33,34,35</sup>

A retrospective survey on the administration of MabThera SC among study nurses involved in the clinical development program was conducted at the end of 2011 to gain

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<sup>28</sup>Shpilberg O. and Jackish C. Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase. *BJC*. 2013; 1-6

<sup>29</sup> Gilbert D. and Cothran D., SC versus IV Delivery: Reducing Costs while Increasing Patient Satisfaction. *Hematology & Oncology News & Issues*, Dec. 25–27, 2005

<sup>30</sup> Haller M.F. Converting Intravenous Dosing to Subcutaneous Dosing With Recombinant Human Hyaluronidase. *Pharmaceutical Technology*. Oct 2, 2007

<sup>31</sup> De Cock E., Kritikou P., Tao S., Wiesner C., Waterboer T. and Carella AM.

<sup>32</sup> NSW Health. 2013. NSW state health plan 2023. Available:

<<http://www.health.nsw.gov.au/statehealthplan/Pages/default.aspx>>. Accessed 16 January 2014 . Accessed 16 January 2014.

<sup>33</sup> Queensland Health. 2013. Health system priorities for Queensland 2013-14. Available:

<[http://www.health.qld.gov.au/hhsserviceagreement/docs/documents/sd1-priority\\_13-14.pdf](http://www.health.qld.gov.au/hhsserviceagreement/docs/documents/sd1-priority_13-14.pdf)>. Accessed 17 January 2014

<sup>34</sup> Department of Health. 2011. Victorian health priorities framework 2012–2022: metropolitan health plan. Available:

<[http://docs.health.vic.gov.au/docs/doc/7BD7DBD50AAEFF8FCA25794B0019A388/\\$FILE/1104014%20VHF\\_2012-22\\_FA7%201%20June.pdf](http://docs.health.vic.gov.au/docs/doc/7BD7DBD50AAEFF8FCA25794B0019A388/$FILE/1104014%20VHF_2012-22_FA7%201%20June.pdf)>. Accessed 17 January 2014

<sup>35</sup> Department of Health. 2013. Victorian health priorities framework 2012-2022: rural and regional health plan. Available: <<http://docs.health.vic.gov.au/docs/doc/Victorian-Health-Priorities-Framework-2012-2022:-Rural-and-Regional-Health-Plan>> Accessed 17 January 2014.

nurses' feedback on different aspects of the administration of MabThera SC.<sup>36</sup> The nurses treated a total of 166 patients, with most nurses (63%) having administered 1 to 5 injections. The majority (72%) reported that SC administration was 'easy' or 'very easy'. Overall, nearly all nurses (95%) rated the overall experience with MabThera SC as 'positive' or 'very positive' and would recommend it to patients (95%).

Assouline et al performed a survey providing some additional information on the patient's experience with MabThera SC as part of the B025341 (SAWYER).<sup>37</sup> Patient and nurse preference questionnaire results after 1 cycle of MabThera SC indicated that the preferred route of administration was SC rather than IV.

Therefore, the SC formulation of MabThera offers several tangible benefits for both patients and healthcare providers:

- Shorter preparation and administration time (approximately 5 minutes)
- Improved patient comfort and convenience
- Lower resource utilisation (for example, nursing time needed for IV administration and patient monitoring, rental of day-beds)
- A simple fixed dose independent of the patient's weight
- An alternative route of administration

Differences in exposure associated with the SC formulation are unlikely to increase the risk of adverse reactions other than local cutaneous reactions.

The MabThera SC development program was designed primarily to compare pharmacokinetic parameters after IV versus SC administration. Safety, including the comparative incidence of reported adverse events after SC versus IV administration, was considered an important secondary endpoint of the studies.

The sponsor acknowledges the Delegate's concern as to whether higher exposure to rituximab translates to worse toxicity profile compared to MabThera IV. However, available data from the SC studies, together with previously published data concerning MabThera IV formulation, indicate that rituximab has a wide therapeutic window and that differences in exposure associated with the SC formulation are unlikely to increase the risk of adverse reactions other than local cutaneous reactions. When designing the MabThera SC studies, it was anticipated that the SC formulation would be associated with local injection site reactions but the safety profile would be otherwise comparable to that of the IV formulation.

Previous experience with the MabThera IV formulation indicates that the safety profile is predominantly a consequence of (i) infusion/administration related reactions and (ii) effects of B-cell depletion discussed further below. In addition the sponsor addresses the concerns of the Delegate in terms of (iii) the proportion of subjects with AEs versus total number of AEs (iv) neutropenia and (v) pneumonitis.

Based on the anticipated safety profile, the number of patients studied is considered sufficient to allow a reasonable assessment of the benefit-risk profile of the SC formulation compared with the IV formulation. Safety data at the time of filing were derived from a

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<sup>36</sup>Sayyed P., Shaw M. and Schnetzler G. Practical experience with a new application mode of rituximab: a retrospective survey on the administration of subcutaneous rituximab among study nurses involved in the clinical development program. *Haematologica* 2012; 97(s1)

<sup>37</sup> Assouline S., Buccheri V., Delmer A., Doelken G., Gaidano G., McIntyre C. et al.

Subcutaneous rituximab in combination with fludarabine and cyclophosphamide for patients with CLL: initial results of a phase 1b study (SAWYER [B025341] show non inferior pharmacokinetics and comparable safety to that of intravenous rituximab. Poster ASH 2013

total of 461 patients across the three MabThera SC studies, 303 of whom received at least one dose of MabThera SC. A total of 1413 doses of MabThera SC were administered.

#### *Local tolerability and infusion/administration-related reactions (ARRs)*

The majority of ARR in the BO22334 study were Grade 1 or 2 and the highest percentage of events occurred during Cycle 1 following the administration of IV MabThera on both treatment arms. The number of patients reporting ARR during Cycle 1 of Study BO22334 following IV administration was higher in the MabThera SC arm (37% [23/62 patients]) than in the MabThera IV arm (29% [19/65 patients]). As anticipated, the incidence of ARR was higher on the SC arm at Cycle 2 following the first SC injection (21% SC versus 6% IV) and to a lesser extent following Cycle 3 (15% SC versus 5% IV) and thereafter decreased to between 5% to 8% [3 to 5 patients] at induction Cycles 4 to 8 on the MabThera SC arm. Four patients (1 [2%] of 65 in the MabThera IV arm and 3 [5%] of 62 in the SC arm) experienced a Grade 3 ARR. It should be noted that two of the SC patients experienced their Grade 3 ARR in Cycle 1 following IV administration. There were no Grade 4 or 5 ARRs.

The sponsor agrees with the Delegate's comment that local tolerability is an important aspect of the overall safety profile and should be taken into account. As such, in the response to the TGA's questions, the sponsor committed to add local cutaneous reactions after SC administration as an 'Identified Risk' to the Risk Management Plan for the product.

#### *Effects of B-cell depletion*

The greater exposure resulting from doses higher than 375 mg/m<sup>2</sup> is not likely to increase the incidence of adverse reactions related to the depth of B-cell depletion. Early dose finding studies of rituximab showed that IV doses of > 100 mg/m<sup>2</sup> resulted in B-cell depletion in most patients.<sup>38</sup> A Phase III study subsequently showed that doses of 375 mg/m<sup>2</sup> once weekly for four weeks caused complete B-cell depletion.<sup>39</sup> Data from the MabThera SC development program confirm that both the BSA adjusted dose of 375 mg/m<sup>2</sup> IV and the fixed dose of 1400 mg SC resulted in effective depletion of B cells following the first IV administration and depletion was maintained following SC administration. It is expected that the duration of B-cell depletion will be similar after the BSA adjusted dose of 375 mg/m<sup>2</sup> and the fixed dose of 1400 mg SC, given that the degree of target saturation and clearance are not influenced by the route of administration. In Study BO22334, the median half-life estimated from the population PK model at Cycle 7 was 33.7 days in the IV cohort and 29.7 days in the SC cohort.

#### *Proportion of subjects with AEs versus total number of AEs*

Inferences concerning the comparative safety of the SC and IV formulations should be based primarily on the proportion of patients who experienced one or more events, rather than on the total number of events in each cohort.<sup>40,41, 42, 43</sup> A difference in the total number

<sup>38</sup>Maloney DG., Liles TM., Czerwinski DK., Waldichuk C., Rosenberg J., Grillo-Lopez A. et al. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. *Blood*. 1994; 84: 2457-2466

<sup>39</sup>McLaughlin P., Grillo-Lopez A., Link BK., Levy R., Czuczman MS., Williams ME. Et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998; 16:2825-2833

<sup>40</sup>Schulz KF, Altman DG., Moher D. CONSORT statement: updated guidelines for reporting parallel group randomized trials. *Brit Med J*. 2010; 340:c332

<sup>41</sup>Moher D., Hopewell S., Schulz KF., Montori V., Gotzsche PC., Devereaux PJ. et al.

Consort 2010 Explanation and elaboration: updated guidelines for reporting parallel group randomized trials. *BMJ*. 2010; 340: c869

<sup>42</sup>Altman DG, Bland JM. Statistics notes: Units of analysis. *BMJ*. 1997; 314 (7098):1874

<sup>43</sup>Bolton S. Independence and statistical inference in clinical trial designs: a tutorial review.

of adverse events between the treatment arms in Study BO22334 was already evident following Cycle 1 when all patients received MabThera IV: 5/65 (8%, 5 events reported) in MabThera IV and 13/62 (21%, 26 events reported). It also appears that females were more susceptible to Grade  $\geq$  3 AEs in Study BO22334 in both treatment cohorts (regardless of route of administration). Grade  $\geq$  3 AEs were reported in 16/32 females (50%, 25 events reported) and 14/33 males (42%, 16 events reported) in the IV cohort and 21/36 females (58%, 61 events reported) and 8/26 males (31%, 11 events reported) in the SC cohort. In Study BO22334, females tended to be older and were more likely to have higher grade lymphoma and high risk FLIPI scores<sup>44</sup> than males. The majority of patients were male in the MabThera IV arm (33/64 [52%]) and female in the MabThera SC arm (37/63 [59%]). This imbalance between treatment arms between males and female may explain some of the apparent difference in the number of reported grade  $\geq$  3 AEs. Nevertheless, the gender effect was consistent within each study irrespective of whether the route of administration was IV or SC.

### *Neutropenia*

To address the Delegate's concern regarding the occurrence of neutropenia in the SC studies the sponsor provides the following analysis. Overall, available data from both MabThera SC studies showed a slightly greater incidence of patients reporting one or more episodes of neutropenia and/or febrile neutropenia in the SC cohort than the IV cohort. Neutropenia and febrile neutropenia events reported in Study BO22334 occurred primarily during induction therapy and is expected in the majority of patients receiving chemotherapy. Neutropenia and/or febrile neutropenia were reported in 24/65 patients (37%) in the IV cohort and 26/62 patients (42%) in the SC cohort. The number of patients whose haematology values worsened and shifted to NCI-CTCAE<sup>45</sup> Grade 3/4 was discussed in the BO22334 clinical study report. The same percentage of patients (20%) in each treatment arm experienced laboratory shifts to Grade 3 neutropenia (13/64 patients in the MabThera IV arm and 12/61 patients in the MabThera SC arm, respectively). In terms of Grade 4 neutropenia, 10/64 patients (16%) in the MabThera IV arm and 12/61 patients (20%) in the MabThera SC arm experienced a worsening neutrophil shift to Grade 4. However, two of the Grade 4 neutropenic episodes in the MabThera SC arm occurred during Cycle 1 (following the patients' first IV MabThera infusion) and therefore it appears that the incidence of neutropenia is very similar following treatment with MabThera IV or SC. Further comparisons of neutropenia and febrile neutropenia as well as late onset and prolonged neutropenia will be performed after completion of Stage 2 of Study BO22334. Several mechanisms for late onset neutropenia associated with rituximab have been postulated, including humoral and cellular immune mechanisms as well as the effects of B-cell recovery on neutrophil kinetics.<sup>46</sup> Based on the pharmacokinetic data from Study BO22334 where the clearance of rituximab was shown to be comparable, B-cell recovery is expected to be similar irrespective of whether the route of administration is IV or SC.

### *Pneumonitis*

In questioning whether increased rituximab exposure translated to worse toxicity, the Delegate specified the reporting of pneumonitis. Whether there is a higher rate of pneumonitis with the SC formulation is unlikely for a number of reasons.

Current knowledge concerning the mechanism of action of rituximab suggests that important long term adverse effects of treatment are the result of immune dysfunction caused by B-cell depletion. Given that the extent and duration of B-cell depletion are

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J Clin Pharmacol. 1998; 38(5):408-412

<sup>44</sup> Follicular Lymphoma International Prognostic Index (FLIPI)

<sup>45</sup> National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE)

<sup>46</sup> Wolach O., Shpilberg O. and Meir L. Neutropenia after rituximab treatment: new insights on a late complication. *Curr Opin Hematol* 2012; 19:32-38

expected to be similar after both SC and IV dosing, it is also anticipated that the incidence of rare, serious events caused by immune suppression will be similar after both IV and SC dosing. It does not seem plausible that differences in the PK profile, including the greater exposure observed in patients after administration of the fixed dose of 1400 mg SC formulation, would result in a greater incidence of adverse effects related to the extent or duration of B-cell depletion itself. The imbalance in pneumonitis events in Study BP22333 is thought to be a chance finding and although two reports were considered related to rituximab treatment, this causal relationship is not a reflection of the route of administration. As discussed above, differences in exposure associated with the SC formulation are unlikely to increase the risk of adverse reactions other than local cutaneous reactions. The safety data for Study BP22333 is influenced by differing degrees of previous MabThera IV treatment before the patients were randomised into the study. Furthermore, these events occurred in the maintenance setting when the relative exposure was lower and no pneumonitis events were reported in Study B022334 on either treatment arm when the relative exposure to rituximab was higher.

#### *Pharmacokinetic-based clinical bridging*

The clinical development program was conducted as a pharmacokinetic based clinical bridging of the MabThera SC formulation versus the IV formulation and was not designed to demonstrate an efficacy benefit. Because the active component is identical in both formulations, serum levels ( $C_{\text{trough}}$ ) after MabThera SC at least as high as after MabThera IV are expected to produce at least the same degree of target saturation and at least the same level of efficacy, irrespective of the route of administration.

In view of the benefit-risk profile of rituximab the prevention of underexposure of all patient subgroups was considered of paramount importance. Therefore Studies BP22333 and B022334 were designed to demonstrate non-inferior pharmacokinetics per the established IV dose for the maintenance and induction dosing intervals, respectively, in order to ensure a rituximab exposure at least as high as after IV. By extrapolation of the pharmacokinetic results, there is no reason to believe that the efficacy of rituximab SC would not translate into comparable efficacy. This assumption was accepted by the clinical evaluator as noted in the Delegate's Overview (see above).

In line with this hypothesis, the overall response rate (ORR) at the end of induction in Study B022334 Stage 1 was 90.5% [80.4%, 96.4%] (SC arm) versus 84.4% [73.1%, 92.2%] (IV arm) and complete response rates (CRR) were 46% [33.4%, 59.1%] and 29.7% [18.9%, 42.4%] respectively. Stage 1 was not designed to show statistical significance in terms of efficacy, however, ORR and CRR point estimates indicate that rituximab's anti-lymphoma activity is not impaired upon SC administration.

Based on  $C_{\text{trough}}$  non-inferiority of MabThera SC 1400 mg compared with MabThera IV 375 mg/m<sup>2</sup> in the induction and maintenance setting and the clinical evidence indicating that SC administration does not impair rituximab's anti-lymphoma activity, the sponsor concludes that the use of MabThera SC 1400 mg can be extrapolated to all established NHL indications where MabThera IV 375 mg/m<sup>2</sup> is approved.

#### ***Nonclinical findings: Pharmacokinetics, recombinant human hyaluronidase page 11:***

*“In the clinical trials, only 1 out of 118 patients had quantifiable levels of hyaluronidase up to 1 h post dose (lower limit of quantification (LLOQ) 0.3125 U/mL), suggesting limited SC bioavailability and rapid clearance in patients.”*

*Sponsor response:* The root cause of the rHuPH20 concentrations found in the blood samples from this patient has since been investigated extensively by the sponsor. The most likely explanation for the observed rHuPH20 levels in the blood samples is thought to be contamination with drug product and not systemic absorption of rHuPH20.

## **Conclusion**

Based on the data provided in the dossier including the additional explanations in this document, the sponsor considers that MabThera SC formulation has a favourable benefit risk profile comparable to that of MabThera IV, while substantially increasing patient convenience and health care resource utilisation. The available data from the SC studies together with previously published data concerning MabThera IV formulation, indicate that rituximab has a wide therapeutic window and that differences in exposure associated with the SC formulation are unlikely to increase the risk of adverse reactions other than local cutaneous reactions. The current data support the registration of MabThera SC formulation in the proposed NHL indications.

## **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 major variations (form and route of administration) for a currently registered product.

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of MabThera [MabThera SC] solution for injection, containing 1400 mg/ 11.7 mL of rituximab (rch). The ACPM considered this product to have an overall negative benefit-risk profile.

In making this recommendation the ACPM

- noted that non-inferiority of the fixed dose SC preparation has been demonstrated compared to conventional IV administration
- expressed concern that the safety profile appears worse, as might be predicted on pharmacologic grounds. SC dosing results in greater exposure to rituximab, particularly among patients with smaller body surface area
- expressed some concern over the lack of data on use over extended periods of time (with projected systemic exposure being substantially increased by approximately 35%)
- noted that while improved patient convenience with the proposed SC preparation has been claimed, this has not been demonstrated. This might become apparent from the second part of Study BO22334 looking at maintenance therapy with SC rituximab as a single agent
  - noted the large volume required for the SC dose.

Following the ACPM meeting, the sponsor was invited to provide comments about the ACPM's recommendations. Following a request from the Delegate, the sponsor submitted new pharmacokinetic, efficacy and safety data from the SABRINA study. This included updated data from patients in Stage 1 as well as data from patients enrolled in Stage 2 of the study.

The data were not evaluated via the normal process, that is, a clinical evaluation report has not been produced. The Delegate's key points are noted below.

Stage 2 planned to assess outcomes at the end of induction and in monotherapy maintenance, in follicular lymphoma. An additional 283 patients were enrolled in Stage 2 (127 had been enrolled in Stage 1). Stage 2 'end of induction' results are available, in a 'top-line' format (that is, not in a full Clinical Study Report format).

The sponsor states regarding *PK results* in Stage 2 (induction setting; q3wk):

Pharmacokinetic results from Stage 2 supported the conclusion of C<sub>trough</sub> non-inferiority of MabThera SC (C<sub>trough</sub> GMR 1.47 [90% CI: 1.28, 1.69]).

This confirms an increase in exposure to rituximab with 1400 mg fixed dosing SC, relative to IV dosing. The following table summarises the PK results.

**Table 8. Observed C<sub>trough</sub> Data at Induction Cycle 7**

C <sub>trough</sub> (µg/mL)	MabThera IV			MabThera SC			Geometric Mean Ratio <sup>b</sup> [90% CI]
	n	Geometric mean	CV (%) <sup>a</sup>	n	Geometric mean	CV (%) <sup>a</sup>	
Stage 1	48	83.13	36.67	54	134.58	43.17	1.620 [1.356, 1.936]
Stage 2	107	79.65	42.52	100	116.02	43.59	1.471 [1.280, 1.690]
Pooled Analysis	155	80.71	40.65	154	122.21	43.82	1.519 [1.362, 1.695]
<b>Body Surface Area</b> (low: BSA ≤ 1.70 m <sup>2</sup> ; medium: 1.70 m <sup>2</sup> < BSA ≤ 1.90 m <sup>2</sup> ; high: BSA > 1.90 m <sup>2</sup> )							
Low	42	85.94	37.04	52	141.49	44.27	1.690 [1.355, 2.108]
Medium	56	84.06	42.49	45	118.04	34.41	1.390 [1.170, 1.651]
High	57	74.05	40.56	57	109.91	40.65	1.492 [1.248, 1.783]

C<sub>trough</sub> values are based upon samples scheduled to be taken 21 days after study drug administration. Samples taken more than 24 hours before or 24 hours after the targeted sampling timepoint were excluded.

<sup>a</sup>Coefficients of variation (CV) calculated on the original scale.

<sup>b</sup>Geometric mean ratio adjusted for tumour load at baseline

(AUC results were not reported in the SABRINA Stage 2 top-line document.)

Regarding *efficacy*, the sponsor states it was pre-planned to analyse ORR and CRR from data pooled from Stage 1 and Stage 2. This is reasonable given study design and treatment arms were identical across stages. In pooled analysis, point estimates for ORR were 84.4% for IV and 83.4% for SC; and for CRR, 31.7% for IV and 32.7% for SC. Stages 1 and 2 showed a *broadly* similar picture. The following table summarises efficacy (ORR) results at end of induction.

**Table 9. Overall response rate at the end of Induction.**

	Overall Response Rate (CR, CRu, PR) at End of Induction [95% CI]		
	MabThera IV + chemo	MabThera SC + chemo	Difference [95% CI]
Stage 1	n = 64 82.8% [71.3%; 91.1%]	n = 63 90.5% [80.4%; 96.4%]	7.66% [-5.0%; 20.3%]
Stage 2	n = 141 85.1% [78.1%; 90.5%]	n = 142 80.3% [72.8%; 86.5%]	-4.82% [-14.0%; 4.4%]
Pooled Analysis	n = 205 84.4% [78.7%; 89.1%]	n = 205 83.4% [77.6%; 88.2%]	-0.98% [-8.4%; 6.4%]
<b>BSA</b> (low: BSA ≤ 1.70 m <sup>2</sup> ; medium: 1.70 m <sup>2</sup> < BSA ≤ 1.90 m <sup>2</sup> ; high: BSA > 1.90 m <sup>2</sup> )			
Low	n = 51 88.2% [76.1%; 95.6%]	n = 77 77.9% [67.0%; 86.6%]	-10.31% [-24.2%; 3.6%]
Medium	n = 77 79.2% [68.5%; 87.6%]	n = 56 85.7% [73.8%; 93.6%]	6.49% [-7.4%; 20.4%]
High	n = 77 87.0% [77.4%; 93.6%]	n = 72 87.5% [77.6%; 94.1%]	0.49% [-11.0%; 12.0%]
<b>Gender</b>			
Male	n = 106 83.0% [74.55%; 89.6%]	n = 86 86% [76.9%; 92.6%]	3.03% [-7.8%; 13.9%]
Female	n = 99 85.9% [77.4%; 92.0%]	n = 119 81.5% [73.4%; 88.0%]	-4.35% [-14.7%; 6.0%]
<b>Chemotherapy</b>			
CHOP	n = 130 86.2% [79.0%; 91.6%]	n = 132 86.4% [79.3%; 91.7%]	0.21% [-8.5%; 9.0%]
CVP	n = 75 81.3% [70.7%; 89.4%]	n = 73 78.1% [66.9%; 86.9%]	-3.25% [-17.0%; 10.5%]

The ORR difference for the low BSA group is despite higher exposure in this group.

In relation to *safety*, the sponsor updated results from Stage 1 (previous median observation time was 8.6 months; now 27.6 months) and provided results from Stage 2 subjects (median observation time of 12.6 months).



With more follow-up of Stage 1 patients, there is now a higher frequency of severe and serious AEs in the IV arm, still consistent with random variation. This longer follow-up must incorporate maintenance (where rituximab is used q8wk). This means pooling (as noted below) will capture induction + maintenance for Stage 1, and only induction (q3wk usage) for Stage 2.

In Stage 2, there was a higher frequency of severe and serious AEs in the SC arm (for Grade 3+ AEs, 40% IV versus 48% SC; for serious AEs, 21% versus 29%). Frequencies of AEs leading to withdrawal (3%) and death (2%) were the same in the two arms.

With pooling of stages, Grade 3+ AEs were reported in 47% (IV) versus 49% (SC) and serious AEs in 26% (IV) vs 29% (SC). Subgrouped by BSA, Grade 3+ AEs were marginally more frequent in low BSA patients given SC rituximab than in low BSA patients given IV rituximab (52% versus 58%). BSA had a stronger correlation than treatment to incidence of severe or serious AEs (patients in the low BSA subgroup were more prone to severe and serious AEs in both arms).

Regarding neutropenia, the sponsor writes of the pooled (Stages 1+2) dataset:

*Neutropenia was reported in 26% of the patients randomized to MabThera IV and 31% of the patients randomized to MabThera SC. Neutropenia was predominantly reported after the first MabThera SC administration, which may indicate a potential reporting bias in this open-label study.*

It is notable that in this new analysis, neutropenia was predominantly reported after the first SC rituximab administration (for example, neutropenia SAEs: 2% IV, 10% SC). Neutropenia events are summarised (in pooled data from Stages 1+2) in the following table.

**Table 10. PT neutropenia events: break down by arm and treatment phase**

<i>Neutropenia</i>	MabThera IV + Chemo (N = 210)			MabThera SC+ Chemo (N = 197)		
	All	SAEs	Grade≥3	All	SAEs	Grade ≥ 3
<b>Induction (1<sup>st</sup> cycle)</b>	19 (9%)	2 (<1%)	12 (6%)	19 (10%)	0	13 (7%)
<b>Induction (cycle 2 - 8)</b>	44 (22%)	1(<1%)	28 (14%)	54 (27%)	5 (3%)	42 (21%)
<b>Maintenance (cycles 9 - 20)</b>	15 (8%)	2 (1%)	11 (6%)	12 (7%)	0	10 (6%)

Thus, the imbalance across arms at Cycle 1 noted for Stage 1 has disappeared in the analysis of pooled results.

The imbalance in serious/severe neutropenia in Cycles 2-8 across arms did not translate into more febrile neutropenia for the SC arm.

While serious/Grade 3+ infections were more common with SC *maintenance*, the SC arm reported more such AEs after *Cycle 1* (where IV rituximab was used across arms), consistent with random variation.

**Table 11. Events corresponding to the SOC Infections and infestations: Break down by arm and treatment phase.**

<i>Infections</i>	MabThera IV + Chemo (N=210)			MabThera SC+ Chemo (N=197)		
	All	SAEs	Grade ≥ 3	All	SAEs	Grade ≥3
<b>Induction (1<sup>st</sup> cycle)</b>	20 (10%)	2 (<1%)	2 (<1%)	22 (11%)	6 (3%)	5 (3%)
<b>Induction (cycle 2 - 8)</b>	80 (39%)	13 (6%)	14 (7%)	88 (45%)	12 (6%)	11 (6%)
<b>Maintenance (cycles 9 - 20)</b>	41 (23%)	0	2 (1%)	46 (27%)	4 (2%)	5 (3%)

Overall, the top-line data update from SABRINA confirms increased exposure to rituximab with the 1400 mg fixed-dose SC approach, similar efficacy (ORR, CRR) outcomes and

broadly similar safety outcomes (excepting more administration-related AEs for SC use and not excluding a modest increase in neutropenia).

### Delegate's conclusions

The only benefit of SC rituximab relative to the existing IV product is 'convenience', though explicit evidence of this benefit is lacking (a concern of the ACPM). Various abstracts summarising research into the convenience of this SC formulation were cited but this level of evidence is not high. The ACPM's view that improved patient convenience is a major factor in favour of approval is noted.

A clear-cut risk of the SC product is worse local tolerability (more administration-related reactions) but this appears clinically manageable.

The Delegate considers that the discussed imbalance in neutropenia seen in B022334 stage 1 is related to baseline imbalances in the two treatment arms. Taking into account the top-line results of B022334 stage 2 (that is, in pooled analysis of both stages), there is a suggestion that the 1400 mg SC approach produces a modestly higher frequency of neutropenia during induction (22% IV versus 27% SC), including a higher frequency of Grade 3+ neutropenia (14% IV versus 21% SC), again seemingly manageable since there was no convincingly large increase in incidence of infection with SC use.

It is 'reassuring' that the three cases of pneumonitis in the same study<sup>47</sup> are clearly infectious.

In regard to the important general concern that increased exposure to rituximab may result in more toxicity, it is reassuring that subgroup analysis by BSA showed no worse toxicity in those with low BSA, in SparkThera. In the updated SABRINA data, there was no convincingly worse toxicity in those with low BSA using the SC approach.

There is absence of evidence of safety around long-term usage. This was a concern of the ACPM. Long term AEs may be related to B cell depletion which is 'complete' with SC and IV approaches, but the sponsor's argument in this regard amounted to assertion.

Possible other risks relate to off-label use (but the fixed dose presentation should mitigate that risk to an extent) and medication error (such as inadvertent IV usage of the SC product).

The Delegate concluded that there is sufficient evidence of quality, efficacy and safety to allow registration of the product. This assumes that:

- The PI will reflect the specific finding that all patients and those with lower BSA in particular will have higher exposure to rituximab.
- The PI will reflect the fact that there is a signal for more neutropenia and an absence of evidence of safety around long-term usage of the SC formulation.

It is noted that *"the Sponsor commits to submit longer term safety and efficacy data available from the BP22333, B022334 and B025341 studies if the application is approved."*

It is noted that *"a further comparison of neutropenia and febrile neutropenia, as well as late-onset and prolonged neutropenia, will be performed after completion of Stage 2 of study BP22333 and study B022334 and the Sponsor has committed to providing updated CSRs from these studies, if the application is approved"*.

In the post Advisory Committee on Prescription Medicines (ACPM) negotiation period, it was agreed with the Delegate that the product name will be "MabThera SC" to differentiate it from the existing IV formulation of MabThera.

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<sup>47</sup>Study SparkThera/BP22333

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of MabThera SC (rituximab rch) solution for injection vial for subcutaneous administration containing rituximab rch 1400 mg/11.7 mL, indicated for:

*For treatment of patients with:*

- *CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,*
- *CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,*
- *CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.*

## Specific conditions of registration applying to these goods

1. The MabThera SC EU Risk Management Plan (RMP), EU-RMP Version 9.1 dated 1 November 2012 with Australian Specific Annex Version 2.0 dated 13 March 2013 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required.

2. It is a condition of registration that, as a minimum, the first five independent batches of MabThera SC rituximab (rch) 1400 mg/11.7mL solution for injection vial (AUST R 207334) imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).
3. An electronic draft of the Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) <<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>>, should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

## Attachment 1. Product Information

The Product Information approved for main MabThera 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

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