Application for the addition of MabThera® (rituximab) 
on the WHO Model List of Essential Medicines

Submitted by 
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1. Summary statement of the proposal for inclusion, change or deletion

F. Hoffmann-La Roche Ltd (Hereafter referred to as Roche) proposes the inclusion of a new formulation for rituximab on the complementary list of the WHO Model List of Essential Medicines (EML) under the category of cytotoxic and adjuvant medicines.

In oncology, Rituximab (brand name MabThera®) is indicated for the treatment of non-Hodgkin’s lymphoma (NHL), chronic lymphocytic leukaemia (CLL). In NHL, MabThera is indicated specifically for follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL).

MabThera for subcutaneous administration (MabThera SC) has been developed as an innovative alternative to the currently licensed IV formulation of MabThera for the treatment of patients with the FL and DLBCL indications of NHL (1400mg) and CLL (1600mg). The SC formulation is indicated for use as a monotherapy or in combination with other medicines, according to the following specifications:

**Non-Hodgkin’s lymphoma (NHL)**
MabThera SC 1400 mg fixed dose formulation is indicated for the treatment of patients with NHL and more specifically:

- untreated stage III-IV follicular lymphoma in combination with chemotherapy.
- follicular lymphoma responding to induction for maintenance regimen.
- CD20 positive diffuse large B-cell NHL in combination with CHOP chemotherapy.

**Chronic Lymphocytic Leukaemia (CLL)**
MabThera SC (1600 mg) is indicated for treatment in adults in combination with chemotherapy of:

- previously untreated and relapsed/refractory CLL.

MabThera SC is an innovative alternative to the intravenous (IV) formulation and enables a less invasive administration of larger volumes of monoclonal antibodies due to the use of a hyperconcentrated solution. MabThera SC uses rHuPH20 technology, a novel excipient that reversibly breaks down hyaluronan, a gel-like substance that forms a barrier in the tissues between cells under the skin, facilitating the dispersion of injected volumes over a greater area (Frost 2007). The administration of MabThera SC requires 5–7 minutes versus 2–4 hours for the infusion of MabThera intravenous (IV) formulation, without compromising its proven efficacy and safety. This enables painless SC administration of MabThera into the abdominal region.

Recombinant human hyaluronidase rHuPH20 has no therapeutic activity (Roche 2012) and does not impair the antilymphocyte activity of MabThera; MabThera SC clinical trials have demonstrated non-inferior MabThera serum concentration after SC injection compared with IV MabThera infusion (Roche 2012).

2. Relevant WHO technical department and focal point (if applicable).

N/A

3. Name of organization(s) consulted and/or supporting the application.

F. Hoffmann-La Roche Ltd

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.
5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate)

MabThera SC is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

MabThera SC contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

Subcutaneous formulation for non-Hodgkin’s lymphoma:
Single dose vials contain 1400 mg/11.7 mL (in 15 mL vial)

Subcutaneous formulation for chronic lymphocytic leukaemia:
Single dose vials contain 1600 mg/13.4 mL (in 20 mL vial)

The safety and efficacy of MabThera in children and adolescents (<18 years) have not been established.

No dose adjustment is required in patients aged ≥65 years of age.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

Individual medicine

7. Treatment details (requirements for diagnosis, treatment and monitoring).

MabThera SC 1400 mg fixed dose formulation is indicated for the treatment of patients with NHL. MabThera SC (1600 mg) is indicated for treatment in adults in combination with chemotherapy of previously untreated and relapsed/refractory CLL.

**Non-Hodgkin’s lymphoma (NHL)**

The recommended dose of MabThera SC used for adult patients is 1400 mg irrespective of the patient’s body surface area, administered through a subcutaneous injection. Before starting MabThera SC, all patients must always receive beforehand a full dose of MabThera by intravenous infusion, using MabThera IV (375 mg/m² body surface area) (Roche 2014).

MabThera should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available (Roche 2014).

In follicular non-Hodgkin’s lymphoma, the recommended protocol for MabThera’s use in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients foresees a first cycle of MabThera IV formulation, followed by 8 subsequent cycles of MabThera SC.

Previously untreated patients who have responded to induction treatment are administered 1400 mg once every two months until disease progression or for a maximum period of two years. A longer interval (three months) is instead used as a maintenance treatment for patients with relapsed/refractory FL who have responded to induction treatment.
In patients affected by diffuse large B-cell non-Hodgkin’s lymphoma, MabThera should be used in combination with CHOP chemotherapy. The recommended dosage is first dose IV followed by 1400 mg per cycle for up to 8 cycles in total.

No dose reductions of MabThera SC are recommended.

**Chronic Lymphocytic Leukaemia (CLL)**

MabThera SC 1600 mg is indicated for the treatment of patients affected by CLL.

MabThera SC is indicated for treatment in adults in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory CLL.

The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is: MabThera IV administered on day 0 of the first cycle of treatment followed by MabThera SC injected at a fixed dose of 1600 mg per cycle, on day 1 of each subsequent cycle (in total: 6 cycles). The chemotherapy should be given after MabThera administration.

All major guidelines recommend the use of MabThera in NHL.

- ESMO Clinical Practice guidelines recommend the use of MabThera for:
  - Newly diagnosed and relapsed follicular lymphoma (FL) (Dreyling 2016).

- The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Oncology include the use of MabThera in the treatment of NHL as category 1 or category 2A across its labelled indications (NCCN 2014).

Both NCCN and ESMO guidelines for the treatment of CLL recommend only treating patients who have active disease (NCCN 2016, Eichhorst 2015).

For patients with active CLL, selection of an appropriate treatment strategy is based on disease stage, patient fitness levels, prior therapy and the presence of negative prognostic factors such as del(17p) and del(11q).

Specific diagnostic and monitoring protocols must be applied in agreement with the current standard of care (SoC) and depend on which indication MabThera is applied to.

- For diffuse large B-cell lymphoma (DLBCL) minimal immunohistochemistry (CD45, CD20, and CD3) is mandatory (Tilly 2016). Surgery is typically carried out for diagnostic purposes; once DLBCL is identified, it is staged to classify disease extension (NIH 2003).
- For patients with follicular non-Hodgkin’s lymphoma (NHL) diagnosis is made on the basis of a lymph node biopsy. FL is classified into cytological grades (grade 1, 2, and 3) based on the number of centroblasts (lymphocytes with a non-cleaved nucleus) in neoplastic follicles using the counting method of Mann and Berard (NCCN 2014). At diagnosis, most patients have grade 1 or 2 disease (Rohatiner 2005).

Diagnosis of CLL is based on three main criteria:

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1. In the NCCN guidelines, recommendations are categorised by levels of evidence and consensus from category 1 (highest evidence and consensus) to category 3 (lowest level of evidence and consensus).
2. Disease characterised by the detection of any of the following symptoms: significant B-symptoms, cytopenia not caused by autoimmune phenomena, symptoms or complications of lymphadenopathy, splenomegaly or hepatomegaly, lymphocyte doubling time of <6 months, autoimmune anaemia and/or thrombocytopenia poorly responsive to conventional therapy.
• Blood count: CLL requires ≥5,000 B-cells/µl in the peripheral blood for a duration of at least three months (Eichhorst 2001; Hallek 2008).
• Blood smear: Leukaemia cells are characteristically small, mature lymphocytes with a narrow border of cytoplasm and dense nuclei that lack discernible nucleoli and have partially aggregated chromatin (Eichhorst. 2001; Hallek 2008).
• Immunophenotype of the circulating lymphoid cells: Co expression of CD5 with CD19, CD20 and CD23 and low levels of slgs, CD79b, CD20 and CD22 (Ginaldi 1998; Moreau 1997).

According to the 2010 ESMO guidelines for the diagnosis and treatment of FL and 2012 ESMO guidelines for DLBCL, initial staging should include a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy (Dreyling 2016; Tilly 2016).

Staging of both FL and DLBCL, usually in accordance with the Ann Arbor staging system, describes the degree to which the lymphoma has spread within the body and is used to determine disease progression. The Ann Arbor staging system reflects both the number of sites of involvement and the presence of disease above or below the diaphragm. At diagnosis, most patients have stage III or IV disease (Tilly 2016; Reiser 2002).

The two staging systems that are used to aid treatment decisions for patients affected by CLL rely on simple clinical examinations and standard laboratory tests (Binet 1977; Rai 1975).

• Revised Rai (more commonly used in the US) stages 0–IV.
• Binet (more common in EU) stages A–C.

Specific tests and protocol can also be used for the determination of prognostic factors that may aid the use of MabThera in clinical practice.

All patients must always receive their first dose of MabThera/Rituxan by intravenous administration in order to avoid an irreversible administration of the full MabThera/Rituxan SC dose during Cycle 1. During this cycle the patient would have the highest risk of experiencing an IRR that can be treated effectively by slowing or stopping the infusion. The subcutaneous formulation must only be given at the second or subsequent cycles. Patients unable to receive the full MabThera/Rituxan IV infusion dose should continue to receive subsequent cycles with MabThera/Rituxan IV until a full IV dose is successfully administered.

For patients who are able to receive the full MabThera/Rituxan IV infusion dose, the second or subsequent MabThera/Rituxan dose can be given subcutaneously using the MabThera/Rituxan SC formulation.

As with the intravenous formulation, MabThera/Rituxan SC should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of a healthcare professional. Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera/Rituxan SC. Premedication with glucocorticoids should also be considered.

Patients should be observed for at least 15 minutes following MabThera/Rituxan SC administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

8. Information supporting the public health relevance.

Diffuse large B-cell lymphoma is the most common type of NHL accounting for >30% of lymphoma incidence (Tilly 2016). FL is the second most frequent NHL subtype, accounting for approximately 20% of the overall NHL incidence (Zinzani 2005, Winter 2004).

According to the 2012 ESMO guidelines, the annual incidence of FL has increased rapidly during recent decades and has risen from 2–3/100,000 during the 1950s to 5–7/100,000 (Dreyling 2016). FL occurs most commonly in middle-aged patients and the elderly, with a median age at diagnosis of approximately 60 years (Rohatiner 2005, Vito 2008). The crude incidence of DLBCL in the EU is 3–4/100,000/year increasing with age from 0.3/100,000/year (35–39 years) to 26.6/100,000/year (80–84 years) (Tilly 2016).
Incidence of FL varies by geographical area, being more common in Western EU and the US, with lower incidence in Asia and developing countries. This difference is paralleled by a lower incidence of the Bcl-2 translocation in patients with FL living in Asia, compared with those in Western countries, which suggests a possible difference in the pathogenesis of the disease (Rohatiner 2005).

CLL is the most common form of adult leukaemia in Western EU, accounting for 25%–40% of all leukaemias (Watson 2008, Ghia 2007, Ikram 2003) with approximately 2–6 new cases in every 100,000 individuals per year (Eichhorst 2011, Ghia 2007). CLL is more prevalent in the elderly, with an estimated median age at first diagnosis reported at 72 years (Horner 2008). In addition, co-existing medical conditions are common in patients with CLL, with one study reporting that almost 90% of patients have at least one co-existing health problem and 46% had at least one major co-existing medical condition (Thurmes 2008).

Although CLL is rare in Eastern countries (such as Japan) and Africa, it is the most prevalent type of leukaemia in Western countries and has a male to female ratio of approximately 2:1 (Ikram 2003).

A study investigating the disease burden of CLL within the EU found that 13,952 individuals were estimated to have prevalent CLL (one-year prevalence estimate, 2006). One, five and ten-year estimates of prevalence in the EU were 0.2, 0.9 and 2.0 per 10,000 individuals, respectively. The results indicate that approximately 46,000 and 107,722 individuals in the EU are living with CLL five and ten years post-diagnosis, respectively, with the highest prevalence being estimated in the Western EU region (Austria, Belgium, France, Germany, Luxembourg and Netherlands) (Watson 2008).
8.1 Roche’s approach to access

At Roche, we strongly believe in the value our medicines bring to patients and their families. Our focus is entirely on developing medicines that meet unmet medical need and we are fully committed to working hard to make sure that those who need our medicines are able to access and benefit from them. We know that our innovation is only truly meaningful when it reaches patients, however we also understand that access to healthcare is a multidimensional challenge and there is no ‘one size fits all’ solution.

From our experience, we believe that awareness, diagnosis, healthcare capacity and funding are determining factors in getting our medicines to patients. Moreover, complex treatments, such as those for cancer, often require sophisticated diagnosis, specialized training and hospital infrastructure for successful treatment. As such, Roche’s Access Planning Framework takes a comprehensive approach, first identifying concrete measures and then addressing country-specific challenges to reach patients. Our goal is to facilitate, broad, rapid and sustainable access to our medicines and with that goal in mind we focus our efforts on capacity building, value recognition, outcome certainty and funding. We partner with stakeholders across the supply-chain and at different health service delivery points to develop and execute tailored solutions.

8.2 Addressing access challenges holistically: Awareness, Diagnosis, Healthcare Capacity and Funding

In recent years, Roche has supported a number of initiatives to help governments increase patient access by enhancing population awareness, health workforce capacity, early diagnosis and developing flexible pricing solutions to alleviate budgetary pressure.

For example, in Colombia, we opened 130 women’s consulting rooms to provide awareness and screening for breast cancer. In Saudi Arabia, we work with the Government and national cancer associations to help educate health workers on examination and diagnosis.

Roche has also brought its oncology expertise to partnerships in insurance to better cover patients for cancer. In China, we teamed up with ten local insurance companies, including the three largest, to help develop additional insurance policies that include cancer treatment and care, and we further developed seminars, forums and campaigns to educate insurers and the wider population about cancer treatment regimens.

Recognising that affordability of innovative medicines can, too, be one of the barriers to access for patients, Roche has developed a differentiated pricing strategy to support countries that have significant access challenges. Our International Differential Pricing (IDP) model aligns innovative medicine prices (including Perjeta - pertuzumab and Kadcyla – trastuzumab emtansine) to a purchasing parity-adapted formula, based on GDP per capita and the Human Capital Development Index, in an individual country. IDP provides significant price flexibility for public healthcare systems in developing countries, facilitating broader and faster access to our medicines, while supporting the sustainability of public healthcare systems.

Roche’s pursuit of global patient access to oncology treatments is not limited to developing countries - it extends to ensure that vulnerable groups in high-income countries also benefit from our technologies. Examples of our work in this field include the efforts to promote increased access in Japan, where Chugai, a member of the Roche Group, donated adapted vehicles to facilitate the transport of senior citizens and people living with a disability to medical facilities; and the financial support provided through our Genentech Access to Care Foundation (GATCF) to ensure access to medicines for US patients who are uninsured or have been denied financial coverage by their insurance provider.

8.3 Measuring the impact of our initiatives is critical

To systematically measure the success of our comprehensive access strategies, we have developed a bespoke system, the Patient Access Dashboard, to measure improvements in access. In 2014, we set out to use this methodology to measure the increase in patient access to two cancer medicines, Herceptin (trastuzumab) and
MabThera (rituximab), in 14 developing countries - representing more than 60% of the population in low and middle-income countries. To support these efforts throughout the organization, we developed a goal to improve access from 29% to 40% of the eligible patient population over a period of four years. At the end of that period in 2017, the goal was exceeded as we were able to increase access to 45%. Based on that success, a new goal for breast cancer medicine, Perjeta, was launched in 2018 in a broader scope of countries.

8.4 Reducing inequality in access

Roche is particularly committed to bringing innovative medicines to low- and middle-income countries and reducing global inequities. In line with this objective, the development of new formulations, like the subcutaneous forms of MabThera and Herceptin, and the clinical trials that we are executing in low-resourced settings, should expand patient access to best standard of care and cancer treatment everywhere. The inclusion of medicines such as Perjeta and Kadcyla, as well as novel formulations of Herceptin and MabThera in the WHO EML 2019 would further support global efforts to increase patient access to important technologies, particularly for HER2 positive breast cancer patients.

Improving global access to healthcare is a Roche core commitment and we recognize how partnership is key to overcoming this challenge. For this reason, we are proud to actively contribute to the global effort of enhancing healthcare access and are keen on making our innovations available for every person who needs and can benefit from them.


Subcutaneous Formulation

Previously Untreated Follicular Non-Hodgkin’s Lymphoma (Davies A 2017)

To investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera SC in combination with CHOP or CVP vs. MabThera IV in combination with CHOP or CVP followed by MabThera maintenance therapy, BO22334 (SABRINA), a two-stage phase III, international, multicenter, randomized, controlled, open-label study was conducted in patients with previously untreated follicular lymphoma.

The overall response at the end of induction was 84.9% in the intravenous group and 84.4% in the subcutaneous group. The frequency of adverse effects was similar in both groups (95% in the intravenous group and 96% in the subcutaneous group); and the frequency of adverse effects of grade 3 or higher was also similar (55% versus 56%, respectively). Neutropenia was the most common grade 3 or higher adverse effect, and occurred in 21% of patients in the intravenous group and 26% in the subcutaneous group. Serious adverse events occurred in 34% of patients in the intravenous group and 37% in the subcutaneous group.

Chronic Lymphocytic Leukaemia (Assouline 2016)

To investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera SC in combination with chemotherapy in patients affected by CLL, BO25341 (SAWYER), a two-part phase Ib, multicenter, randomized, open-label, parallel-group study was conducted in patients with previously untreated CLL. The objective of Part 1 was to select a MabThera SC dose that resulted in rituximab serum C_{trough} levels comparable to those obtained with MabThera IV. The dose of 1600 mg of MabThera SC was selected for Part 2 of the study. The objective of Part 2 was to establish non-inferiority in observed rituximab C_{trough} levels between the selected MabThera SC dose and the reference MabThera IV dose.

Response rates were similar for the MabThera IV and SC arms, with an overall response rate of 80.7% (95% CI: 70.9; 88.3) and 85.2% (95% CI: 76.1; 91.9) in the MabThera IV and SC arms, respectively. Complete response rate point estimates were 33.0% (95% CI: 23.3; 43.8) and 26.1% (95% CI: 17.3; 36.6) in the MabThera IV and SC arms, respectively. Overall the results confirmed that MabThera SC 1600 mg has a comparable benefit/risk profile to that
of MabThera IV 500 mg/m². The most common adverse event of grade 3 or higher was neutropenia (56% in the subcutaneous group and 52% in the intravenous group).

9.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/inclusion of particular data)

The history of rituximab, its mechanism, and the clinical trials conducted have been reviewed in an article by Pierpont and colleagues (2018). The review summarises all the main clinical trials conducted and explains the basic molecular mechanisms, which are at the base of rituximab mechanism of action. The work highlights that the introduction of rituximab has noticeably improved the outcomes of patients affected by diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia. Despite this, still area of urgent medical needs persist.

The authors underline that research into mechanisms and potential biomarkers of rituximab response is still ongoing, since the exact mechanism of action in each indication is not clear. This lack of comprehension is reflected in the absence of companion diagnostics, which would help better identify different populations of patients (Pierpont 2018).

9.2 Summary of available data (appraisal of quality, outcome measures, summary of results)

The following studies describe the clinical development of MabThera SC for B-cell malignancies:

- SparkThera was a randomised, open-label, phase Ib study designed to investigate the PK, safety and tolerability of the MabThera SC formulation as part of maintenance treatment in patients with FL. The study comprised a dose-finding phase and a dose-confirmation phase. A dose of MabThera SC 1400 mg was established as having non-inferior MabThera Ctrough values and comparable area under curve (AUC) levels to those observed with MabThera administered intravenously.

- SABRINA (BO22334) was the pivotal phase III randomised, open-label, international, multi-centre study in patients with previously untreated FL followed by maintenance treatment. The study was designed to assess non-inferiority between MabThera SC 1400 mg and MabThera IV in terms of two co-primary endpoints: pharmacokinetics (PK) and efficacy (overall response rate [CR (complete response), CRu (unconfirmed complete response) and PR (partial response)] after completion of induction therapy). Determination of a MabThera SC dose was ascertained in a phase Ib study (BP22333, SparkThera).

- MabCute is an ongoing, multi-centre, randomised, parallel group, phase IIIb study, designed to evaluate the efficacy and safety of long-term use of MabThera SC 1400 mg versus observation in patients with relapsed or refractory indolent Non-Hodgkin Lymphoma (iNHL). MabThera SC 1400 mg was well tolerated with no new safety signals or concerns identified during induction and maintenance therapy, as confirmed by the Independent Data Monitoring Committee.

- MabEase was a Phase IIIb, prospective, multi-centre, multinational, open-label randomised study to estimate the efficacy of MabThera SC 1400 mg and IV, both in combination with Cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy, in 572 adult patients with previously untreated CD20-positive DLBCL. Overall, the efficacy, safety and tolerability profile of SC or IV in this study was generally consistent with the findings previously observed with SC or IV, and with MabThera plus cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) safety profile. In terms of patient-reported outcomes, the RASQ showed a higher satisfaction with SC.

- SAWYER was a two part, randomised, open-label, parallel-group, multi-centre, phase Ib study of MabThera SC 1600 mg versus IV, both in combination with chemotherapy (fludarabine, cyclophosphamide (FC)), in patients with previously untreated CLL (Roche 2016). It was designed to confirm a MabThera SC dose predicted from SparkThera and confirm the pharmacokinetic non-inferiority of the selected SC dose (1600 mg), compared with MabThera IV. Overall, in addition to the comparable overall response rate (ORR) between MabThera IV and SC, the results from time-to-event analyses further support similar efficacy
between MabThera IV and SC. In the context of the totality of the data, including the efficacy data of SABRINA, the switch to the SC route of administration does not impair the anti-B-cell activity of MabThera.

Results from these trials in MabThera show that MabThera SC provides non-inferior PK (\(C_{\text{trough}}/\text{AUC}\)), as well as comparable efficacy and safety to MabThera administered intravenously:

### 9.2.1 Pharmacokinetics
- The SparkThera trial (Stage 1) showed that a fixed dose of MabThera SC 1400 mg two monthly (q2m) or three monthly (q3m) would achieve non-inferior MabThera \(C_{\text{trough}}\) values and comparable AUC levels to those observed with MabThera administered intravenously at 375 mg/m\(^2\) IV q2m or q3m. (Salar 2014)
- SparkThera Stage 2 confirmed the non-inferiority of \(C_{\text{trough}}\) for the SC formulation compared with the IV formulation, as the lower bounds of the 90% confidence intervals were demonstrated to be above the pre-specified non-inferiority boundary of 0.8. (Salar 2014)
- SABRINA reported that the drug concentration in the blood was comparable between the SC formulation and the IV formulation with pooled (from Stage 1 and Stage 2) geometric mean \(C_{\text{trough}}\) (SC)/\(C_{\text{trough}}\) (IV) ratio ([90% CIs]) of 1.52 [1.36;1.70] and AUC (SC)/AUC (IV) ratio of 1.38 [1.24;1.53]. (Davis 2014a & 2014b)

### 9.2.2 Pharmacodynamics
- In SparkThera (Stage 1), available data from patients at the nine month follow-up visit showed an increase in B-cell levels at this time point compared with previous time points, with median counts of 0.05 (Cohort A, \(n = 6\)), 0.03 (Cohort B, \(n = 16\)), 0.02 (Cohort C, \(n = 15\)), and 0.03 × 109 cells/L (Cohort D, \(n = 7\)). Among those patients enrolled in Stage 2 an increase in B-cell levels could also be seen. (Salar 2014)

### 9.2.3 Efficacy
- The SAWYER trial (Part 1) demonstrated that the incidence of patients that experienced a progression-free survival (PFS) or event-free survival (EFS)-related event was similar across all sub-cohorts, and the incidence of death (overall survival (OS)-related event) varied among all sub-cohorts. Due to the low number of patients in each sub-cohort interpretation of the results should be made with caution. (Roche 2016)
- In SAWYER Part 2, the results of the time-to-event analyses were comparable across treatment arms. The hazard ratio of PFS was 0.89 (95% confidence interval (CI): 0.49;1.64), the hazard ratio of EFS was 0.76 (95% CI: 0.44;1.33), and the hazard ratio of OS was 0.60 (95% CI: 0.24;1.52); all of which demonstrated a wide CI crossing 1, indicating no substantial difference in benefit to either the IV or SC 1600 mg arms. (Roche 2016)
- The SABRINA trial (Stage 2) reported that the point estimate for complete response (CR/CRu) was numerically higher in the IV arm compared with the SC arm (34.8% [95% CI: 26.9, 43.2] versus 28.2% [95% CI: 20.9, 36.3]), whereas the rate of PR was similar between the two arms (50.4% [95% CI: 41.8, 58.9] versus 52.1% [95% CI: 43.6, 60.6]). (Davis 2014; Davis 2014a & 2014b)
- The SABRINA trial (Stage 2) reported a higher proportion of patients in the IV arm (85.1%; 95% CI: 78.1, 90.5) achieved an overall response (CR, CRu, and partial response (PR)) compared with patients in the SC arm (80.3%; 95% CI: 72.8, 86.5). (Davis 2014a & 2014b)

### 9.3 Summary of available estimates of comparative effectiveness

#### 9.3.1 The Sabrina Study (BO22334) (Davies A 2017)
Results of the pivotal clinical trial SABRINA (BO22334) showed that MabThera SC 1400 mg provides non-inferior PK (\(C_{\text{trough}}/\text{AUC}\)), as well as comparable efficacy and safety to MabThera administered intravenously. The point estimate for complete response (CR or CRu) was numerically higher in the IV arm compared with the SC 1400 mg arm (34.8% [95% CI: 26.9, 43.2] versus 28.2% [95% CI: 20.9, 36.3]).
A higher proportion of patients in the IV arm (85.1%; 95% CI: 78.1, 90.5) achieved an overall response (CR, CRu, and PR) compared with patients in the SC 1400 mg arm (80.3%; 95% CI: 72.8, 86.5), whereas the rate of partial response was similar between the two arms (50.4% [95% CI: 41.8, 58.9] versus 52.1% [95% CI: 43.6, 60.6]).

The primary objective of Stage 1 was to estimate the ratio of trough serum concentration of MabThera obtained at cycle 7, 21 days after SC administration to that obtained after IV administration (C_{trough(SC)}/C_{trough(IV)} during cycle 7 of induction treatment). Stage 2 aimed to further investigate the efficacy and safety of MabThera SC 1400 mg compared with MabThera IV. The primary end points were:

- PK for Stage 1
- ORR at end of induction for Stage 2

The secondary endpoints were: PK, safety, efficacy (CRR, PFS, EFS and OS, ORR at end of maintenance), healthcare provider-reported convenience.

The results of the primary and secondary analyses at study snapshot were as follows:

- Based on investigator assessments, ORR was comparable in both treatment arms (83.4% for SC 1400 mg arm and 84.4% for IV), indicating that the SC route of administration did not impair MabThera’s anti-lymphoma activity.
- Complete response rates at the end/completion of induction were also similar (32.7% and 31.7% for SC 1400 mg and IV, respectively).
- Response results were confirmed by independent radiologists (~92% concordance with investigator-assessed ORR for both treatment arms).
- Limited maintenance phase data were available; however, the proportion of patients with an objective response was numerically similar between treatment arms in the maintenance phase (43.8% for IV versus 44.4% for SC 1400 mg).
- Other secondary efficacy endpoints, including PFS, event-free survival (EFS), and OS were immature.
- C_{trough} at cycle 7 in the Stage 2 and in the pooled ITT population supported the Stage 1 PK conclusion that MabThera SC 1400 mg is non-inferior to IV 375 mg/m² when given every 3 weeks in combination with CHOP or CVP (pooled geometric mean ratio [C_{trough(SC)}/C_{trough(IV)}]: 1.52 [90% CI: 1.36, 1.70]).
- There were no new clinically relevant safety signals observed with MabThera SC 1400 mg compared with the Stage 1 analysis. The safety profile of MabThera SC 1400 mg was generally comparable to that of MabThera IV.
- Data on B-cell levels (CD19+ counts) showed similar trends in both treatment arms, with significant depletion of peripheral B-cells following cycle 1 (IV) and continued depletion with additional cycles in the induction and maintenance phases.

Physicians and nurses who administered SC 1400 mg felt that at least one to three hours could be saved by using the SC 1400 mg formulation in routine clinical practice, and 86% felt strongly that SC 1400 mg formulation is much more convenient than the IV formulation.

### 9.3.2 The SparkThera Study

SparkThera (BP22333) was a randomised, open-label, phase Ib study designed to investigate the PK, safety and tolerability of the MabThera SC formulation as part of maintenance treatment in patients with FL. The study comprised a dose-finding phase (Stage 1) and a dose-confirmation phase (Stage 2).

Patients with FL grade 1, 2, or 3a who achieved at least a partial response (PR) after induction treatment comprising four cycles or more of MabThera as monotherapy or in combination with chemotherapy, and had received at least one cycle of MabThera administered intravenously (375 mg/m²) in the maintenance setting as part of a q2m or q3m regimen, were enrolled into Stage 1 initially, and subsequently into Stage 2 once the SC dose was selected. A central randomisation procedure was used for all patients that fulfilled the entry criteria at screening. A block-based randomisation method stratified by maintenance regimen (q2m or q3m) was used for both stages.

The results of the SparkThera Study are summarized in Table 1 and Table 2.
**Table 1. SparkThera: Summary of predicted $C_{\text{trough}}$ data - Stage 2**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Predicted MabThera $C_{\text{trough}}$ (μg/mL)</th>
<th>Mean ratio $C_{\text{trough}}(\text{SC})/C_{\text{trough}}(\text{IV})$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric mean [95% CI]</td>
<td>[90% CI]</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>SC</td>
</tr>
<tr>
<td>q2m</td>
<td>25.92 [21.45;31.32]</td>
<td>32.22 [27.98;37.10]</td>
</tr>
</tbody>
</table>

SC: Subcutaneous; IV: Intravenous; q2m: two-monthly; q3m: three monthly; CI: Confidence interval.

**Table 2. SparkThera: Summary of predicted AUC data - Stage 2**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Predicted MabThera AUC$\tau$ (μg/day/mL)</th>
<th>Mean ratio AUC$\tau(\text{SC})/AUC\tau(\text{IV})$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric mean [95% CI]</td>
<td>[90% CI]</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>SC</td>
</tr>
<tr>
<td>q2m</td>
<td>4012 [3721;4326]</td>
<td>5430 [4980;5921]</td>
</tr>
<tr>
<td>q3m</td>
<td>3947 [3662;4255]</td>
<td>5320 [4880;5799]</td>
</tr>
</tbody>
</table>

SC: Subcutaneous; IV: Intravenous; q2m: two-monthly; q3m: three monthly; Confidence interval.

**9.3.3 The SAWYER Study**

SAWYER (BO25341) was a two part, randomised, open-label, parallel-group, multi-centre, phase Ib study of MabThera SC versus MabThera IV both in combination with chemotherapy (FC), in patients with previously untreated CLL. The SAWYER study was required in addition to the SparkThera study as it was necessary to bridge individually different MabThera doses and dosing intervals. Part 1 (dose selection) of SAWYER was designed to confirm that a MabThera SC dose, predicted from SparkThera based on modelling and simulation, would result in $C_{\text{trough}}$ levels comparable to MabThera IV. SAWYER Part 2 (dose confirmation) confirmed the pharmacokinetic non-inferiority of the selected SC dose (1600 mg), compared with MabThera IV 500 mg/m.

**Part 1 Results**

**Composition of Progression-Free Survival.** At time of analysis, 37.5%, 41.2% and 30.4% patients in the MabThera SC 1400 mg, 1600 mg, and 1870 mg sub-cohorts, respectively, had experienced progression-related events (disease progression/relapse or death, whichever occurred first).

The Kaplan–Meier curves are similar and overlapping for the MabThera sub-cohorts until month 24, at which time greater variability is noted. Because of the low number of events at the time of the update analysis, the median PFS time could not be estimated for any of the MabThera sub-cohorts.

**Composition of event-free survival.** At the time of analysis, 37.5%, 41.2% and 30.4% patients in the MabThera SC 1400 mg, 1600 mg, and 1870 mg sub-cohorts, respectively had experienced an event (initiation of new anti-leukaemic treatment, disease progression/relapse, or death, whichever occurred first). Of those patients who experienced an event, 14.3% patients in the MabThera SC 1600 mg sub-cohort and no patients in the MabThera SC 1400 mg and 1870 mg sub-cohorts initiated new anti-leukaemic treatment. Half of the patients in the MabThera SC 1400 mg sub-cohort and 71.4% each in the MabThera SC 1600 mg and 1870 mg sub-cohorts experienced progression/relapse. Death due to any cause was 50.0% in the MabThera SC 1400 mg sub-cohort, 14.3% in the MabThera SC 1600 mg sub-cohort, and 28.6% in the MabThera SC 1870 mg sub-cohort.

**Composition of Overall Survival.** At the time of analysis, 18.8%, 5.9% and 13.0% patients in the MabThera SC 1400 mg, 1600 mg, and 1870 mg sub-cohorts, respectively had died. The Kaplan–Meier curves are similar and overlapping for the MabThera sub-cohorts until Month 24, at which time greater variability is noted. Because of the low number of events at the time of the update analysis, the median OS time could not be estimated for any of the sub-cohorts.

**Part 2 Results**

**Composition of Progression-Free Survival.** At the time of analysis, the incidence of progression-related events (disease progression/relapse or death, whichever occurred first) was similar in the MabThera IV and SC arms.
(26.1% and 21.6% patients, respectively). The hazard ratio was 0.89 (95% CI: 0.49;1.64) with a wide confidence interval crossing 1 indicating no substantial difference in benefit to either the IV or SC arms.

Among patients who experienced an event, 69.6% patients in the MabThera IV arm and 89.5% patients in the MabThera SC arm had experienced progression/relapse. Death occurred in 30.4% of patients in the MabThera IV arm and 10.5% of patients in the MabThera SC arm.

**Composition of Event-Free Survival.** At the time of analysis, the incidence of events (initiation of new anti-leukaemic treatment, disease progression/relapse, or death, whichever occurred first) was similar in the MabThera IV and SC arms (33.0% of patients and 25.0% patients, respectively). The hazard ratio was 0.76 (95% CI: 0.44;1.33) with a wide confidence interval crossing 1 indicating no substantial difference in benefit to either the IV or SC arms.

**Composition of Overall Survival.** At the time of analysis, a total of 19 patients had died: 13.6% in the MabThera IV arm and 8% patients in the MabThera SC arm. The hazard ratio was 0.60 (95% CI: 0.24; 1.52) with a wide confidence interval crossing 1 indicating no substantial difference in benefit to either the IV or SC arms. The Kaplan–Meier curves are similar and overlapping for the two treatment arms. Because of the low number of events at the time of the update analysis, the median OS time could not be estimated for either treatment arm.


10.1 Estimate of total patient exposure to date

The estimated cumulative clinical trial exposure to rituximab from the DIBD (22 December 1992) and until 17 November 2017 is 17,626 patients. Since the 26 November 1997, the estimated cumulative market exposure to rituximab until 30 September 2017 is 5,898,480 patients, of which 520,320 patients were estimated to have received rituximab during the reporting interval (Roche 2017).

10.2 Description of the adverse effects/reactions and estimates of their frequency

The following section details the undesirable effects of MabThera SC, as laid out in Section 4.8 of the EMA MabThera SC and IV SPCs (Roche 2012, Roche 2014).

During the development programme, the safety profile of MabThera subcutaneous formulation was comparable to that of the intravenous formulation, with the exception of local injection site reactions. Local injection site reactions were very common in patients receiving MabThera subcutaneous formulation in trials SparkThera (BP22333) and SABRINA (BO22334), reported in up to 50% of patients at some time during treatment. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritis and rash. The vast majority of the reactions following subcutaneous administration were mild or moderate.

**10.2.1 Adverse reactions reported in MabThera subcutaneous formulation usage**

The risk of acute reactions associated with the subcutaneous formulation of MabThera was assessed in two open-label trials involving patients with follicular lymphoma during induction and maintenance (SABRINA BO22334) and during maintenance only (SparkThera BP22333).

- In trial BO22334, severe administration-related reactions (grade ≥3) were reported in two patients following administration of MabThera subcutaneous formulation (one patient reporting grade 3 injection site rash, and one patient reporting grade 3 dry mouth), both occurring after induction cycle 2 i.e. the first MabThera subcutaneous formulation dose given to each patient.
- In trial BP22333, no severe administration-related reactions were reported.

**10.2.2 Adverse reactions reported in MabThera intravenous formulation usage**

The overall safety profile of MabThera IV formulation in NHL and CLL is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.
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The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera IV were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of MabThera.

Infectious events (predominantly bacterial and viral) occurred in approximately 30–55% of patients during clinical trials in patients with NHL and in 30–50% of patients during clinical trials in patients with CLL.

The most frequent reported or observed serious adverse drug reactions were:

- Infusion related reactions (including cytokine-release syndrome, tumour-lysis syndrome)
- Infections
- Cardiovascular events

Other serious ADRs reported include hepatitis B reactivation and PML.

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. The incidence of infusion-related symptoms decreased substantially with subsequent IV infusions and is <1% of patients by the 8th cycle of MabThera (containing) treatment.

### 10.3 Summary of available data (appraisal of quality, summary of results)

Table 3 summarizes the available data on ADRs both in clinical trials and postmarketing surveillance in patients with NHL and CLL treated with MabThera monotherapy/maintenance or in combination with chemotherapy (Roche 2014).

Table 3. Summary of the available data on ADRs both in clinical trials and postmarketing surveillance in patients with NHL and CLL treated with MabThera monotherapy/maintenance or in combination with chemotherapy.

<table>
<thead>
<tr>
<th>Frequency of ADRs</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Bacterial infections, viral infections, bronchitis, neutropenia, leucopenia, febrile neutropenia, thrombocytopenia, infusion-related reactions, angioedema, nausea, pruritus, rash, alopecia, fever, chills, asthenia, headache, decreased IgG levels.</td>
</tr>
<tr>
<td>Common</td>
<td>Sepsis, pneumonia, febrile infection, herpes zoster, respiratory tract infection, fungal infections, infections of unknown aetiology, acute bronchitis, sinusitis, hepatitis B, anemia, pancytopenia, granulocytopenia, hypersensitivity, hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia, paraesthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety, lacrimation disorder, conjunctivitis, tinnitus, ear pain, myocardial infarction, arrhythmia, atrial fibrillation, tachycardia, cardiac disorder, hypertension, orthostatic hypotension, hypotension, bronchospasm, respiratory disease, chest pain, dyspnea, increased cough, rhinitis, vomiting, diarrhea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation, urticaria, sweating, night sweats, skin disorder, hypertonia, myalgia, arthralgia, back pain, neck pain, pain, tumour pain, flushing, malaise, cold syndrome, fatigue, shivering, multi-organ failure.</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy, depression, nervousness, dysgeusia, left ventricular failure, supraventricular tachycardia, ventricular tachycardia, angina, myocardial ischaemia, bradycardia, asthma, bronchiolitis obliterans, lung disorder, hypoxia, abdominal enlargement, infusion site pain.</td>
</tr>
<tr>
<td>Rare</td>
<td>Serious viral infection, pneumocystis jirovecii, anaphylaxis, severe cardiac disorders, interstitial lung disease.</td>
</tr>
<tr>
<td>Very rare</td>
<td>PML, transient increase in serum IgM levels, tumour lysis syndrome, cytokine release syndrome, serum sickness, peripheral neuropathy, facial nerve palsy, severe vision loss, heart failure, vasculitis (predominantly cutaneous), leukocytoclastic vasculitis, respiratory failure, gastrointestinal perforation, severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome), renal failure.</td>
</tr>
<tr>
<td>Not known</td>
<td>Late neutropenia, infusion-related acute reversible thrombocytopenia, cranial neuropathy, loss of other senses, hearing loss, lung infiltration.</td>
</tr>
</tbody>
</table>

10.4 Summary of comparative safety of subcutaneous versus intravenous formulations

With the exception of local cutaneous reactions including injection site reactions, the safety profile of MabThera/Rituxan SC was otherwise comparable to that of the IV formulation. No cases of anaphylaxis or severe hypersensitivity reactions, cytokine release syndrome or tumour lysis syndrome were observed following subcutaneous administration during the MabThera/Rituxan SC development program.

**10.4.1 SABRINA (BO22334) (Davies 2014):**

Pooled data from Stage 1 and Stage 2 of the Sabrina study demonstrated similar incidences of patients with at least one AE (92% and 93%), AE of grade ≥3 intensity (47% and 49%), and SAEs (26% and 29%) for IV and SC 1400 mg, respectively. The incidence of patients with ARRs was higher in the SC 1400 mg treatment arm (47% versus 33% in IV). However, ARRs were predominantly mild to moderate local injection site reactions, such as mild pain, swelling, and erythema, as expected when switching to the SC route of administration.

Some numerical differences of specific AEs were observed, and it is possible that there may have been potential reporting bias in this open-label study. Of note, neutropenia was reported in 26% of patients randomised to IV and 31% of patients randomised to SC 1400 mg (the difference being driven by higher reporting of neutropenia after the first SC 1400 mg administration). However, clinically relevant AEs associated with neutropenia, such as febrile neutropenia and severe infections, were balanced between the SC 1400 mg and IV treatment arms. Additional exploratory analyses did not reveal any subgroup with noticeable safety differences when comparing SC 1400 mg with IV.

**10.4.2 SparkThera (BP22333): Safety assessment**

In the SparkThera study, safety assessments included AEs, standard laboratory assessments, and vital signs. The numbers of events reported were similar across the cohorts (26 AEs Cohort A; 36 AEs Cohort B; 36 AEs Cohort C; 30 AEs Cohort D). The number of patients that reported administration-related reactions (ARR) was higher among patients that were administered MabThera via SC injection (1 ARR Cohort A, 8 ARRs Cohort B, 13 ARRs Cohort C, 13 ARRs Cohort D), however all ARRs were Grade 1 or 2 in intensity.

The number of patients experiencing AEs was the same in both treatment groups (61/77 patients [79%] per group). The proportion of patients with grade ≥3 AEs was comparable across treatment groups (18% SC versus 17% IV). Besides grade ≥3 neutropenia (2 patients SC, 2 patients IV), the incidence of other grade ≥3 AEs reported was no more than 1% (i.e. 1 patient). The proportion of patients who experienced SAEs was comparable across treatment groups (12% SC versus 14% IV). Eight patients experienced AEs leading to withdrawal from treatment (4 patients [5%] per group), half of whom withdrew due to serious AEs (2 SC and 2 IV).

**10.4.3 SAWYER (BO25341) (Assouline 2015)**

**10.4.3.1 Part 1 results**

The safety population included all patients who received a per-protocol MabThera SC dose in cycle 6 (n=55). Comparison of AE profiles for MabThera SC and IV was restricted to cycles 5 and 6 because patients could have enrolled at any time during cycles 1–4. Three patients withdrew from the study after cycle 5, but prior to receiving MabThera SC, due to AEs (neutropenia [n=2] and Guillain-Barré syndrome [n=1]).

There was a slight increase in the number of AEs reported during cycle 6 (n=36; 64%) versus cycle 5 (n=32; 54%). The majority of AEs were grade 1 or 2 and the most commonly reported in both cycles were neutropenia and leucopenia. Patients who received higher SC doses experienced more AEs (n=7; 44%, n=10; 59% and n=18; 82% for 1400 mg, 1600 mg and 1870 mg, respectively). However, a similar pattern was observed in cycle 5 (IV administration).
More patients experienced ARRs during cycle 6 (n = 12; 21%) compared with cycle 5 (n=2; 3%) for all three doses of MabThera. The most frequently occurring ARRs in cycle 6 were pain (n=4; 7%) and erythema (n = 3; 5%) at the injection site; all were grade 1 or 2.

10.4.3.2 Part 2 results

In the safety population, 96% of patients given MabThera SC 1600 mg and 91% of patients given MabThera IV had at least one AE, the most common of which were neutropenia and nausea. Rates of AEs were similar between groups in cycle 1, when patients in both groups received MabThera IV, and in cycles 2-6. More patients in the SC 1600 mg group than the IV group had AEs in the system organ classes general disorders and administrative site conditions (driven by higher incidences of the preferred terms injection-site erythema, pyrexia, and injection-site pain), skin and subcutaneous tissue disorders (driven by higher incidences of erythema and pruritus), and musculoskeletal and connective tissue disorders (driven by higher incidences of arthralgia, bone pain, and pain in extremity). More patients in the IV group than the SC 1600 mg group had vascular disorders (driven by higher incidences of hypotension and hypertension).

Rates of AEs of grade 3 and higher were similar between groups overall and during cycle 1. During cycles 2-6, more patients in the SC 1600 mg group than the IV group had AEs of grade 3 and higher, driven by a higher incidence of leukopenia (n=11 [13%] versus n=4 [5%]).

The frequency of SAEs was similar between groups. The most common SAE, febrile neutropenia, was more often reported in patients in the SC 1600 mg group than in those in the IV group (n=9 [11%] versus n=7 [8%]); however, the incidence of febrile neutropenia of any grade was similar between groups. The most common AE leading to discontinuation was neutropenia (n=1 in the SC group, n=3 in the IV group). In seven (44%) patients, the AE causing treatment withdrawal was deemed to be treatment related (neutropenia, thrombocytopenia, and urticaria in one patient each in the SC group; neutropenia in two patients and febrile neutropenia and acute renal failure in one patient each in the IV group).

Nine (5%) patients died (n=5 in the SC 1600 mg group and n=4 in the IV group); five deaths (n=3 and n=2, respectively) were due to progressive disease and four deaths (two in each group) were due to AEs (herpes zoster infection and progressive multifocal encephalopathy, both MabThera related, in the SC 1600 mg group and diarrhoea and listeriosis, neither MabThera related, in the IV group).

The proportion of patients reporting local cutaneous reactions in the SC 1600 mg group decreased over treatment cycles 2-6 (cycle 2: 32%; cycle 3: 25%; cycle 4: 17%; cycle 5: 6%; cycle 6: 7%), as did the intensity of reactions. No patient discontinued treatment because of local cutaneous reactions.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

The prices of our medicines reflect the benefits they deliver to patients, society and healthcare systems. When we price our medicines, we consider a number of factors, including the clinical benefit relative to available alternatives, the level of medical need addressed and the ability of healthcare system and individuals to afford our products. We recognize that there are differing healthcare needs and affordability challenges in developing countries as well as in developed markets which may prevent people from having access to our medicines. That's why our pricing approach allows our affiliate to address their country-specific needs. Ultimately, the price of a medicine in the majority of markets is the outcome of a negotiation with local payers. We are therefore committed to finding flexible pricing solutions that support payer's reimbursement decisions and help us to meet the needs of patients and other stakeholders.

11.1 Cost-savings of rituximab subcutaneous (SC)

For the treatment of indolent B-cell non-Hodgkin's lymphoma (iNHL) and subtypes of diffuse large B-cell lymphoma (DLBCL) the combination therapy with intravenous (IV) infusion of rituximab and chemotherapy has
demonstrated superiority to chemotherapy alone with respect to overall survival (Knight 2004, Schulz 2007, Gao 2010, Fang 2010). However, IV administration takes approximately three to four hours which can incur high costs on patients, health care professionals (HCP) and the health care system. Subcutaneous (SC) formulation can be administered via hand-held syringe in less than ten minutes plus follow up time and thus has the potential to realize considerable cost savings.

The phase Ib Sparkthera trial showed non-inferiority of rituximab SC compared with rituximab IV administered as maintenance therapy in terms of trough serum concentrations and overall response rates in patients with iNHL (Salar 2010, Salar 2014). The two-stage, phase 3, multi-center, randomized, controlled, open-label SABRINA trial in follicular lymphoma demonstrated that IV and SC rituximab had similar efficacy and safety profiles, and no new safety concerns were noted. SC administration does not compromise the anti-lymphoma activity of rituximab when given with chemotherapy (Davies 2017).

A time and motion study by De Cock et al. (2016) illustrated that the use of subcutaneous administration can bring considerable time savings for both, healthcare professionals (HCP) and patients (Table 4). The estimated time savings per administration can transform into an annual reduction in active HCP time (time actively dedicated by any staff member to pre-specified tasks) of 1.1-5.2 hours depending on the local administration process. Patient chair time (time between entry and exit of infusion chair) was decreased by 53-91% translating into absolute time savings in the first year of treatment of 3.1-5.5 eight-hour days.

Table 4: Administration duration of rituximab SC and rituximab IV and comparison

<table>
<thead>
<tr>
<th></th>
<th>Intravenous (IV)</th>
<th>Subcutaneous (SC)</th>
<th>Time savings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rituximab [minutes]</td>
<td>rituximab [minutes]</td>
<td>In %</td>
</tr>
<tr>
<td>Mean time for healthcare professionals (HCP)</td>
<td>35</td>
<td>23.7</td>
<td>-32%</td>
</tr>
<tr>
<td>Mean patient chair time (PCT)</td>
<td>262.1</td>
<td>67.3</td>
<td>-74%</td>
</tr>
</tbody>
</table>

Source: De Cock et al. (2016)

From a health care system perspective, less HCP time per administration of rituximab may increase the efficiency of the provision of care HCP as time-savings allow hospital staff to spend more time on other patient care activities, and thus increase the overall staff efficiency, improve medical outcomes for patients and save costs in the health care system. For patients, a lower chair time offers the opportunity to invest saved time in other activities.

Because rituximab IV dosing is based on body surface (mg/m²), while rituximab SC dosing is fixed, the drug acquisition costs of SC formulations can also be lower than acquisition costs of IV formulations in patients who are heavier than a critical body weight (Figure 1).
12. Summary of regulatory status and market availability of the medicine.

MabThera 1400 mg solution for SC injection for the treatment of patients with NHL was first approved on 21 March 2014, in the EU, and has since been approved in more than 60 other countries including the US.

A further dose strength of this formulation (MabThera 1600 mg solution for SC injection) for the treatment of patients with CLL was approved on May 25, 2016, in the EU, and has since been approved in more than 20 other countries including the US. Submissions and regulatory reviews in other countries are ongoing for both dose strengths.


There are no pharmacopoeial standards specific for MabThera. The drug product does comply with the European Pharmacopoeia monographs, “Pharmaceutical Preparations (2619)”, “Parenteral Preparations (0520)”, and “Substances for Pharmaceutical Use (2034)”.

14. Comprehensive reference list and in-text citations.

Application for the addition of MabThera® (rituximab) on the WHO Model List of Essential Medicines

- Davies A, Barrett M, Berge C. Primary Clinical Study Report – Protocol BO22334 – A two-phase stage III, international, multi-center, randomized, controlled, open-label study to investigate the pharmacokinetics, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in patients with previously untreated follicular lymphoma followed by maintenance treatment with either rituximab SC or rituximab IV – Report No. 1058994 2014b.
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- Roche. Summary of product characteristics for MabThera SC. 2014.
- Roche. Update Clinical Study Report – BO25341 An Adaptive, Comparative, Randomized, Parallel-Group, Multi-Center, Phase Ib Study of Subcutaneous (SC) Rituximab versus Intravenous (IV) Rituximab both in Combination with Chemotherapy (Fludarabine and Cyclophosphamide) in Patients with Previously Untreated CLL. June 2016.
- Roche. PSUR (PBRER) rituximab – 18th Nov. 2016 to 17th Nov. 2017 - F. Hoffmann-La Roche Ltd Report Number 1081698.
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### Appendix 1

#### Summary of regulatory status and market availability of MabThera®

<table>
<thead>
<tr>
<th>Country</th>
<th>Worldwide market approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1400 mg (NHL indications)</td>
</tr>
<tr>
<td>Albania</td>
<td>February 2015</td>
</tr>
<tr>
<td>Argentina</td>
<td>May 2015</td>
</tr>
<tr>
<td>Aruba</td>
<td>November 2014</td>
</tr>
<tr>
<td>Australia</td>
<td>May 2014</td>
</tr>
<tr>
<td>Bahrain</td>
<td>November 2017</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>November 2017</td>
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<tr>
<td>Belarus</td>
<td>April 2015</td>
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<tr>
<td>Bolivia</td>
<td>April 2015</td>
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<td>Bosnia-Herzegovina</td>
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<td>Brazil</td>
<td>December 2015</td>
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<tr>
<td>Cambodia</td>
<td>April 2018</td>
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<td>Canada</td>
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<td>Chile</td>
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<td>Colombia</td>
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<td>July 2015</td>
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<td>Cuba</td>
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</tr>
<tr>
<td>Curacao</td>
<td>June 2015</td>
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<tr>
<td>Dominican Republic</td>
<td>July 2015</td>
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<td>Ecuador</td>
<td>December 2015</td>
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<td>Egypt</td>
<td>October 2018</td>
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<td>El Salvador</td>
<td>March 2015</td>
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<td>March 2014</td>
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<td>Georgia</td>
<td>October 2014</td>
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<td>Ghana</td>
<td>April 2018</td>
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<td>Kazakhstan</td>
<td>November 2016</td>
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Application for the addition of MabThera® (rituximab) on the WHO Model List of Essential Medicines

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