2013 LeIP REPORT CARD ON LYMPHOMAS

LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

Lymphoma eInformation Project (LeIP)

The cycle – develop therapy, fight to have it approved and then fight to have it funded – cannot continue as it currently stands, it is not working.

ABOUT LYMPHOMA COALITION

The Lymphoma Coalition (LC) is a global patient network of 58 lymphoma patient organisations from 43 countries with a mission to be the global source for lymphoma facts and statistics; to improve awareness and understanding of lymphomas; and to build capacity for new and existing groups.

The Coalition continually disseminates information on all lymphomas including CLL, to ensure that members are kept up to date on advocacy policy, therapy access, lymphoma research and demographics.

Our goal is to encourage the best patient care around the world with the end goal of saving more lives.

SPECIAL THANKS to all the lymphoma patients and the LC member organisations who offered their insight and support as well as to the many other organisations, government agencies, pharmaceutical companies, pharmacists and individuals who generously shared their knowledge, resources and understanding for this report.

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CONTENTS

A MESSAGE FROM THE EXECUTIVE DIRECTOR

Karen Van Rassel
Executive Director
Lymphoma Coalition

Lymphoma Coalition's (LC) strength lies in its unique ability to bring the global lymphoma patient organisation network together within an effective platform to share best practice, educational information, as well as to collectively advocate for change.

In last year's report card, standard of care, clinical trials, treatment availability and demographics on both a global scale and at the local level were discussed. This report takes us a step further into a look at regulatory and funding/reimbursement process and procedures. We asked this question, are therapies getting to patients in a timely and cost-effective manner?

A full report summarising our findings comparing different regulatory and funding/reimbursement procedures as well as a summary flow chart for each of the LC member countries support the report card. Please visit the LC website to view this information or scan the code at the back of the report.

LC is privileged to partner with the INTERLYMPH Consortium and their latest findings on risk factors and causes of lymphoma are included. Thank you to the over 100 international members of the consortium for working together to compare research results and expand on the excellent work being done in centres all over the world.

Thank you to Shawn Sajkowski for your hundreds of internet research hours and discussions with many organisations from all over the world and to Leonie Bedford for the compilation and analysis of the research resulting in the following 2013 LeIP Report Card on Lymphomas.

Let's continue to support the patient by being vigilant rather than complacent; never stop raising awareness about lymphoma and the needs of patients with lymphoma. When decisions have to be made, think first, how will this affect the lymphoma patient?

A MESSAGE FROM THE CHAIR OF THE LC MEDICAL ADVISORY BOARD

Dr. Laurie Sehn, MD, MPH
Chair, BC Cancer Agency Lymphoma Tumour Group
Clinical Associate Professor at the University of British Columbia, Vancouver, Canada
Chair, LC Medical Advisory Board

The last decade has brought rapid and significant advances in the management of lymphoma. Advancements in molecular biology have lead to greater biologic insight into the underlying mechanisms of disease, which in turn has translated into the development of a vast array of novel targeted therapies with encouraging potential. While many new drugs are now clinically available, a larger number are being actively investigated in clinical trials and have demonstrated promising efficacy. The rate at which these agents are proceeding through the development process appears to be accelerating, and has been aided by the commitment of organizations such as the US Food and Drug Administration, with the establishment of a "breakthrough therapy" fast track.

While this is an exciting time for lymphoma research and care, it has brought the issue of access to the forefront. The 2013 LeIP Report Card on Lymphomas by the Lymphoma Coalition focuses on the drug approvals and funding process in a large number of countries with affiliated member organizations. The goal was to elucidate the various steps involved in the approvals process and to identify the barriers that result in delays or restrictions in drug availability. The compiled report serves to highlight the universal challenges being faced with respect to regulatory lags and funding constraints. The report also demonstrates notable disparities between countries with respect to timelines and access. This comprehensive review should serve as a valuable resource which can be used to compare and contrast the systems in place and also serve as a tool to guide process change as we strive toward our common goal of achieving better outcomes for lymphoma patients.

A MESSAGE FROM THE ACTING CHAIR OF THE LC BOARD OF DIRECTORS

Pru Etcheverry
CEO, Leukaemia & Blood Cancer New Zealand
Acting Chair, LC Board of Directors

The Lymphoma Coalition (LC) continues to grow in size and to mentor patient organizations around the world through its mission and goals. It is important to understand the systems within which we need to work to ensure that therapies are getting to the patients, and in a timely and cost-effective manner.

The 2013 LeIP Report Card on Lymphomas clearly demonstrates that lymphoma patients and the member organisations that support them face widely differing challenges. Across different regions of the world there is great variance within regulatory frameworks. Regrettably for some patients in some countries access to comprehensive diagnostic services, malignant haematology expertise, good hospital services and drug supply schemes as well as infrastructure to support research-based medicine remains out of reach.

LC aims to track these measurable data further and to evolve this into tracking access to funded therapies. We hope this second annual LeIP report card will provide LC members and patients with the evidence to advocate for improvement in their own organisations and countries. We envisage that in time these reports with support from the LC will help tackle patient needs – for every person in the world living with lymphoma – and lead to better survival and quality of life.

LYMPHOMA COALITION
Worldwide Network of Lymphoma Patient Groups

2013 LeIP REPORT CARD ON LYMPHOMAS

Lymphoma eInformation Project (LeIP)

OVERVIEW

Great advances have been made in the treatment of lymphomas with new developments occurring regularly that should, in theory, provide doctors and patients with many more options when it comes to determining the optimal therapy for patients with lymphoma. With this progress, however, we are confronted with a problem of affordability. Governments and other payers are struggling to find ways to fund or reimburse the cost of therapies and, more importantly, many patients cannot afford them. Given world economic turmoil, governments are reducing their costs by cutting budgets for all sectors including healthcare. And the squeeze on government budgets is likely to worsen as the population ages and the demands on healthcare systems grow.

One of the Lymphoma Coalition's (LC) goals for the 2013 Lymphoma eInformation Project (LeIP) Report Card was to determine how patients with lymphoma are affected by the changes in healthcare. Specifically, we wanted to determine if patients with lymphoma receive therapy in the most cost-effective and timely manner. **Through its research, the LC discovered that there are a myriad of barriers preventing therapies from reaching patients in a timely and cost-effective way.** Systems (regulatory and funding) are often cumbersome, slow and difficult to access. Within countries, there are multiple layers of approvals with review bodies often appearing to be independent fiefdoms rather than cohesive units that can accept information from one body without having to undertake their own review of the same information. This contributes to enormous time lags between the submission of a drug for regulatory approval and then funding approval. Both regulatory and funding approval timelines can stretch into years.

Therapies being considered by review bodies are for patients who may have a life-threatening illness and who are likely in desperate need for the very therapies under review. Input from patients and patient advocacy groups is critical in the regulatory and funding review processes. **Both patients and patient advocacy groups need to play an active role to ensure that the impact of the decision on the patient is taken into account.**

LC's findings are somewhat disheartening, but the hope is that as a community we can work together to find ways to improve patients' lives in spite of governments' best intentions to keep healthcare costs down, the escalating costs of targeted therapies and payers' struggle to meet the demand.

Objectives

LC undertook a review of the regulatory and funding processes for all member organisation countries. For this report card, however, LC focused its analysis on 11 countries and the European Union (EU); namely Australia, New Zealand, Switzerland, France, Germany, the United Kingdom (UK), United States of America (USA), Canada, Spain, Brazil and Argentina to determine what efforts are made to ensure therapies reach patients with lymphoma in a timely and cost-effective manner. These 11 countries and the EU were chosen in order to provide a regional sample. Flow charts showing the regulatory and funding review processes for all member organisations as well as the full review can be found on the LC website (http://www.lymphomacoalition.org/global-report) or scan the code at the back of the report.

The objectives of the analysis were to:

- Provide LC member organisations with, at the very least, a top-line awareness of how other regulatory and funding processes work in order to speak confidently on changes taking place in their own countries;
- Determine if there are roadblocks in the systems that prevent treatment getting to patients in a timely and cost-effective manner;
- Determine best practices, i.e., which countries have relatively straightforward drug approval as well as funding/reimbursement processes and compare them with those that do not.

To address the objectives of this review, this report card focuses on three issues:

1) Timelines, i.e., the length of time for a drug to be approved;
2) Layers of approval, i.e., the number of times the same information is reviewed;
3) Funding/reimbursement, i.e., who pays for the drug.

LC anticipated two other factors that may have been roadblocks in getting therapies to patients in a timely and cost-effective manner: fees (what it costs to get a drug approved) and whether or not a clinical trial had to be conducted in the country as part of the regulatory process. In investigating fees and the clinical trials execution process, it was found that, for the most part, they were not roadblocks. It should be noted, however, that LC would like to see fees reduced as a way of increasing affordability for patients.

Australia appeared to be the only country studied in this review where, as part of the regulatory approval process for a drug, a clinical trial had to be conducted in its own country in order for the drug to be approved. The reasons cited for undertaking clinical trials in Australia are that they provide clinicians with an opportunity to gain experience using a drug and they have to include a cost-effectiveness component, something not required by either the Food and Drug Administration (FDA) or the European Medicines Agency (EMA). However, when the LC searched clinicaltrials.gov to see how many trials were being undertaken in lymphoma, of the 495 trials found, Australia was only participating in 52. This means that patients in Australia are likely missing out on having access to new and better therapies.

Methodology

The goals of the 2013 LeIP Report Card were accomplished through:

- Review and comparison of regulatory and funding processes for cancer drugs in the EU and the11 countries already mentioned. These countries were chosen as they are viewed as being representative of their geographic region;
- Reviewing information available on the internet and verifying its accuracy through published journals, interviews with LC member organisations, representatives of the pharmaceutical industry and review bodies;
- Gathering information on regulatory and funding processes by country and recording it in a flow chart. To view the flow charts go to the LC website (http://www.lymphomacoalition.org/global-report) or scan the code at the back of the report. In the development of these charts, more than 500 websites were accessed and approximately 1,200 hours were spent on research.

This report card provides highlights of LC's findings. Readers are encouraged to visit the LC website to read the full report as well as separate, more detailed flow charts for each country, and a matrix that compares common denominators among countries such as drug approval application costs, levels of approval, and the length of time involved in both the regulatory and funding processes at http://www.lymphomacoalition.org/global-report or scan the code at the back of the report.

Definitions

Regulatory Process and Procedures

Before a therapy can be sold/proposed to a patient, its efficacy, tolerability and safety have to be assessed by the country's respective regulatory body to ensure that it not only provides benefit but that it can be safely used in humans. Each country has its own process for undertaking this review.

Therapy Funding/Reimbursement Process and Procedures

Once a drug has been approved, the usual next step is to determine if it will be funded/reimbursed, i.e., who will reimburse or partially reimburse patients who have been prescribed the therapy or what government body will fund a therapy. The types of bodies that may help with funding are government agencies, private payers and, at times, drug manufacturers.

Note: All times shown are in business days. Business days are calculated at 20 per month.

KEY FINDINGS & DISCUSSION

In an effort to combat rising costs, governments not only evaluate a new therapy for its efficacy, safety and tolerability, but also its cost effectiveness in comparison with similar drugs that have already been approved to ensure it provides value for dollars spent. And while such cost-effectiveness assessments may show benefit, the therapy may still not be funded because cost and/or funding decisions made at the national level are not necessarily adopted at the regional or local level. Additionally, the length of time it takes for regulatory and funding reviews to be completed will have a negative impact on patients

TABLE 1: ECONOMIC OVERVIEW RANKED BY GDP PER CAPITA

Country	GDP per capita, US$[4]	Per capita spending on health based on OECD data, US$[5]	GDP ranking among 56 LC member organisations*	Healthcare expenditure as % of GDP, %[1]	Healthcare expenditure ranking among 56 LC member organisations*	Population[4]
Switzerland	54,600	5,914†	2	10.9	7	7,925,517
USA	49,800	8,507‡	3	17.9	1	313,847,465
Australia	42,400	3,800§	4	9.0	18	22,015,576
Canada	41,500	4,666†	8	11.2	4	34,300,083
Germany	39,100	4,494‡	9	11.1	6	81,305,856
UK	36,700	3,405†	12	9.3	15	63,047,162
France	35,500	4,117‡	14	11.6	3	64,612,939
Spain	30,400	3,072‡	16	9.4	12	47,042,984
New Zealand	28,800	3,182‡	18	10.1	10	4,327,944
Argentina	18,200	___**	26	8.1	22	42,192,494
Brazil	12,000	___**	35	8.9	19	199,321,413

GDP = gross domestic product; LC = Lymphoma Coalition; OECD = Organisation for Economic Co-operation and Development; UK = United Kingdom; USA = United States of America
*As of July 2013; †2012 data; ‡2011 data; §2010 data; **Argentina and Brazil not included in OECD data set

Table 1 provides an economic snapshot of the countries reviewed in this report. Based on the information in the table, healthcare expenditure as a percentage of gross domestic product is highest in the USA at 17.9% and lowest in Argentina at 8.1%.[1] Yet, as the report card will show, a country's wealth does not necessarily correlate with healthcare that is easily accessible as well as affordable. For example, in the USA, approximately 84 million people had either no health insurance or exorbitant out-of-pocket health expenses that they were underinsured at some point in 2012.[2] In Argentina, where payers are required by law to cover all cancer therapies at no cost to the patient, payers make every effort to delay providing such coverage and patients often have to resort to legal action.[3]

The following are the key findings from the research along with a table and figure that illustrate some of the seemingly convoluted processes and procedures that take place in the approval as well as funding/reimbursement review processes for new therapies. For the full report go the LC website (http://www.lymphomacoalition.org/global-report) or scan the code at the back of the report.

1. Timelines

The timeline for approving a drug varies from country to country. None of the review processes (either regulatory or funding/reimbursement), with the exception of the USA's FDA regulatory review process, are particularly timely. For example, someone living in New Zealand could wait up to 1,267 days, maybe longer, before having access to an approved as well as funded therapy.[6,7] Someone living in England/Northern Ireland could wait up to 1,050 days.[8,9] Numerous factors likely have an impact on the approval timelines but one factor that has a definite impact is the number of review phases in both the regulatory and funding/reimbursement processes (see Table 2).

The regulatory review undertaken by the EMA is considerably slower than that undertaken by the FDA. Cancer therapies intended for use in the European Union (EU) have to first be reviewed and approved by the EMA. According to Roberts et al., many times patients have to wait longer for therapies because applications are typically submitted to the FDA first.[10] Once applications are submitted to the EMA, the reported median review time was 350 versus 120 days in the USA. Another reason for the longer approval timeline in the EU is that there are two steps that have to be taken before a drug can be sold: first, the EMA Committee for Medicinal Products for Human Use must issue a positive opinion on marketing authorisation, i.e., the drug is approved for use in humans; second, this opinion has to be adopted by the European Commission.[10]

An example of the impact of this difference is shown by the length of time to approve lenalidomide (Revlimid). The FDA took 264 days to approve it; the EMA 387 days. In this instance, applications were made to the FDA and the EMA at the same time (January 2003). Another example is bortezomib (Velcade). The FDA review time was 112 days; EMA 358 days. Applications were submitted to the FDA in April 2005 and to the EMA in February 2006.[10] Keep in mind that once the EMA and the FDA have provided approval, it does not necessarily mean the patient can receive the drug. The EU member countries have to issue their own approval as well as undertake funding and reimbursement reviews. Depending on the EU country, it can be another 111 to 392 days before a patient can access therapy.[11] In the USA, funding and reimbursement reviews are undertaken by public payers (Centers for Medicare & Medicaid Services, Department of Defense and Department of Veterans Affairs), private payers and individual states, respectively.

In Switzerland, patient access to new treatments is often delayed because the applicant may wait to submit a new drug application to the Swiss Agency of Therapeutic Products (Swissmedic) until after the EMA has issued its marketing authorisation as often the same dossier is used in the application. Given that it takes the EMA 350 days[10] to approve an oncology drug and review and approval by Swissmedic can take up to 420 days, it could be 770 days before a drug is approved. When factoring in the amount of time the funding review body takes (between 100 and 120 days), it could be up to 890 days before a patient receives a funded treatment.[12]

Australia's approval systems (regulatory and funding) are viewed as time consuming and complex comprising numerous assessments within each phase.[13] For example, within the regulatory approval process there are eight phases with two of the phases being assessment phases following which there is an expert advisory review phase which may, in turn, seek information from other committees. If all steps are followed it can take between 240 and 260 days for a drug to receive regulatory approval. And, by the time the funding review process is completed and the drug is listed on the Pharmaceutical Benefits Scheme, it can be another 280 days; in essence, a patient has had to wait at least 520 days before receiving therapy. More information is provided later in this report card on the layers of approval in Australia.

Other countries whose funding review times can be considered exceptionally long include the UK and Germany. In the UK, before funding and reimbursement reviews can begin, the Medicines and Healthcare Products Regulatory Agency (MHRA) has to review all new drug applications. This can take between 60 to 120 days.[12] This review is then followed by a review by the National Institute for Health and Clinical Evaluation (NICE) for England and Northern Ireland (up to 520 days),[8,9] the Scottish Medicines Consortium (SMC) for Scotland (154 days)[8,14] and the All Wales Medicines Strategy Group (AWMSG) for Wales (520 to 645; Wales waits to see if NICE will issue its guidance within 240 days; if it takes longer then Wales undertakes its own review).[15] These bodies undertake their own reviews to determine whether or not to fund the therapy; part of the review entails looking at the effectiveness of the therapy. Hence, it could be anywhere from 154 to 645 days before funding or reimbursement for an EMA-approved therapy is in place in the UK and a patient with lymphoma can access the therapy.

In Germany, while reimbursement is determined automatically following approval by the EMA and all new cancer therapies are then theoretically available immediately under both the statutory health insurance (GKV) and the private health insurance (PKV), in reality, they are not available until the budgeting process is completed, which can take up to 440 days.[8] So, if the EMA has taken 350 days[10] to approve a therapy and it takes 440 days to complete the budgeting process, that makes it 790 days BEFORE a therapy is available in Germany.

By reducing timelines, it would likely be possible to reduce the cost of getting therapies to market and, consequently, reduce the cost to patients.

Table 2 provides an overview of the review bodies involved in regulatory and funding/reimbursement processes, as well as the number of steps or phases required in each process. When looking at the table spend a few moments identifying the redundancies.

2. Layers of Approval

Adding to the time it takes for a drug to receive both regulatory and funding approval are the number of approval bodies involved in how the drug will come to market. Most of the delays pertain to the number of steps or phases involved in the funding review process (see Table 2). **But, what is perhaps more important, is how often the same information is reviewed before a funding decision is made. As a result, it is often an unacceptable length of time before a patient can receive treatment**. A number of countries provide excellent illustrations of this issue.

Canada is a prime example where the same information is reviewed by bodies at both the federal and provincial/territorial level. All drug applications are reviewed by Health Canada. In addition, if an applicant wants their therapy funded by a government agency, an application has to be made to the pan-Canadian Oncology Drug Review (pCODR). Health Canada examines the drug's efficacy, safety, quality, labelling and marketing information[33]; pCODR examines the clinical evidence and the cost effectiveness (neither of these bodies communicates directly with the other, all communication is done via the applicant).[34] Once Health Canada has issued marketing authorisation and pCODR made a funding recommendation, the provinces then undertake their own reviews to decide whether to fund the drug. Keep in mind, that pCODR is funded by all provinces except one. The funding review process undertaken by each of the 10 provinces and three territories varies but comprises an average of three steps; typically, provincial timelines are not known. Not a very satisfactory situation for a patient waiting for treatment.

The process followed by England and Northern Ireland is another example. Pixantrone (Pixuvri) is a good illustration of the many layers involved in approving a drug. A therapy for non-Hodgkin B-cell lymphoma, pixantrone was approved by the EMA for use in patients whose cancer had relapsed or was refractory to other therapies. NICE, in its initial appraisal, indicated that pixantrone should not be recommended within its marketing authorisation for treating relapsed or refractory aggressive NHL as the benefit of pixantrone had not been established.[12]

So, it begs the question: what was the point of submitting to the EMA only to have NICE say something else? Figure 1 illustrates the layers of review as well as the lengthy time it takes for decisions to be made. Keep in mind that while the number of steps or phases in the MHRA review is unclear, the NICE process comprises 10 phases/steps.

FIGURE 1: PIXANTRONE REIMBURSEMENT PROCESS[12]*

May 2012	⇨	EMA approves pixantrone
August 2012	⇨	Application submitted to MHRA
November 2012	⇨	Dossier submitted to NICE
March 2013	⇨	MHRA approves application
April 2013	⇨	NICE issues first negative funding opinion
July 2013	⇨	NICE to consider new evidence in September 2013
October 2013	⇨	NICE issues second negative funding opinion

EMA = European Medicines Agency; MHRA = Medicines and Healthcare Products Regulatory Agency; NICE = National Institute for Health and Clinical Excellence
*Information as of October 2013

As the chart shows, it's a long drawn out process to have a therapy funded in England and Northern Ireland. Another demonstration of a system whereby a therapy does not get to the patient in a timely and cost-effective manner.

While review bodies had to be formed to ensure that therapies coming to market were efficacious as well as safe and funding put in place, questions need to be asked; namely: are all the review bodies and phases needed? Are there functions that can be done by one review body as opposed to two or three? **Every time a new review body or phase is added, what needs to be considered is whether there is any duplication of effort as well as the impact it will have on the patient outcome.**

3. Funding/Reimbursement

When it comes to funding/reimbursement there is great variability among the countries studied. In a study that examined the reimbursement level of licensed indications for 10 cancer drugs including bortezomib (Velcade) and rituximab (Rituxan, MabThera), it was found that Canada, Australia, Scotland, England and New Zealand had the most restricted access to publicly funded drugs with the lowest level of reimbursement compared with France, Germany and

TABLE 2: OVERVIEW OF REVIEW BODIES AND APPROVAL TIMES

Unless otherwise stated, all times are actual in business days

COUNTRY	REGULATORY				FUNDING/REIMBURSEMENT			
	# of review bodies	# of phases/ steps	What review bodies do	Actual time, days	# of review bodies	# of phases/steps	What review bodies do	Actual time, days
USA	1[16]				Funding provided by public payers (CMS [responsible for Medicare, Medicaid, CHIP], VA, DoD), private payers and individual states[8]			
	FDA	7	Reviews efficacy, safety, quality	Priority: 158 Std.: 198[17]				
EU	5				Funding decisions by each European Union member country – see below			
	EMA[18]	1	Reviews efficacy, safety, quality	410[19]				
	CHMP	3	Validates application	10*				
	Rapporteur	1	Undertakes scientific assessment	140*				
	PRAC	1	Conducts risk assessment					
	EU	3	Adopts opinion of EMA	±67*				
England/ Northern Ireland	2				1			
	EMA[18]	1	Reviews efficacy, safety, quality	410[19]	NICE[8,9]	10	Reviews clinical and cost effectiveness	Up to 520
	MHRA[20]	Information not available	Reviews safety monitoring, AE reporting, drug distribution, marketing materials	60-120*[12]				
Scotland	2				1			
	EMA[18]	1	Reviews efficacy, safety, quality	410[19]	SMC[8,14]	8	Reviews clinical effectiveness; undertakes economic assessment	154
	MHRA[20]	Information not available	Reviews safety monitoring, AE reporting, drug distribution, marketing materials	60-120*[12]				
Wales	2				1			
	EMA[18]	1	Reviews efficacy, safety, quality	410[19]	AWMSG[15]	10	Reviews clinical effectiveness; undertakes economic assessment	125*†
	MHRA[20]	Information not available	Reviews safety monitoring, AE reporting, drug distribution, marketing materials	60-120*[12]				
France	1				4[21]			209[9]
	EMA[18]	1	Reviews efficacy, safety, quality	410[19]	TC	4[22]	Determines medical benefit and improvement of medical benefit vs. std. of care	
					CEPS	Information not available	Reviews improvement of medical benefit, compares pricing with other countries, negotiates price with applicant	
					Health Minister	Information not available	Approves application	
					UNCAM	Information not available	Sets reimbursement rate for national funding	
Germany	1				3[8,23]			Up to 440
	EMA[18]	1	Reviews efficacy, safety, quality	410[19]	G-BA	4	Determines drug reimbursement	
					IQWiG	8	Assesses benefit. For orphan drugs: no review by IQWiG; only review by G-BA required[24]	
					GKV-SV	3	Negotiates reimbursement price with applicant	
Spain[21]	2				3[21,25]			349[11]
	EMA[18]	1	Reviews efficacy, safety, quality	410[19]	DGFPS/MoH	2	Approves drug; adds to national reimbursement list	
	AEMPS	1	Issues national product code	Information not available	CIPM	2	Undertakes pharmacoeconomic assessment; negotiates price with applicant	
					GCPT	1	Develops advice report for CIPM	
Switzerland	1				2			111[11]
	Swissmedic[12,21]	5	Reviews efficacy, safety, quality	Priority: 140* Std.: 220-420*	FOPH[12]	3	Makes reimbursement decision	
					FDC	1	Reviews application based on cost effectiveness of existing therapies, compares international prices, gives reimbursement recommendation to FOPH	
Canada	1				2			99-149*‡
	Health Canada[26]	4	Reviews efficacy, safety, drug labelling, marketing information	Priority: 180* Std.: 356[19]	pCODR (national body)[27]	9	Reviews cost effectiveness, clinical evidence	
					Provincial/territorial approvals	2-6	Assesses budget impact, clinical evidence and effectiveness	Information not available
Australia	1				3			At least 280[13]
	TGA[28]	8	Reviews efficacy, safety, quality	240-260*	PBAC (see chart at www.lymphomacoalition.org)	9	Assesses clinical and cost effectiveness	
					PBPA	3	Assesses clinical and cost effectiveness	
					MoH	2	Determines financial and feasibility acceptability	
New Zealand	2				2			±720[6]
	MEDSAFE[29]	4	Reviews efficacy, safety, quality	Std: 365-547[7] Priority: No exact timeline[7]	PHARMAC[30]	8	Undertakes economic assessment, reviews cost effectiveness	
	MoH[29]	1	Makes decision based on MEDSAFE recommendation		PTAC	4	Reviews proposal, requests CaTSoP advice, makes recommendation, reviews priority of proposals	
Brazil	3				3			
	ANVISA[31]	2	Inspects facility; grants marketing authorisation	Priority: 180 Std.: 280-480	CONITEC[32]	2	Reviews efficacy, safety, cost effectiveness	180
	GEPEC	1	Undertakes pharmacological, safety and efficacy evaluations		MoH	1	Makes funding decision	Information not available
	CMED	1	Negotiates price with applicant		National, state, municipal		Makes funding decision	Information not available
Argentina	1				3			
	ANMAT[12]	5	Provides Provision check and signature; gives assignation date and number to Provision	140[12]	Public payers[12]		Case by case negotiation between applicant and funding body	45-60
	• Registration office		Evaluates application, samples, CPP		Semi-private[12]		Each case may need to be negotiated; depends on the payer	30-45
	• Drug Evaluation Department		Undertakes medical evaluation		Private[12]		Depends on the payer and how much information payer needs	±30
	• Legal Department		Evaluates evidence of commercialisation, manufacturer, application form, CPP					
	• Technical Secretariat		Provision check, signature					
	• Dispatch Department		Assignation date, number to Provision					

*Reported review time; actual time unknown; †Wales follows NICE guidance if published within 220 days; otherwise undertakes own review; ‡Does not include provincial funding approval time; see detailed chart on LC website (www.lymphomacoalition.org/global-report) or scan the code at the back of the report

AE = adverse event; AEMPS = Spanish Medicines Agency; ANMAT = National Administration of Drugs, Food and Medical Technology; ANVISA = Brazilian Health Surveillance Agency; AWMSG = All Wales Medicines Strategy Group; CaTSoP = Cancer Treatments Subcommittee of PTAC; CEPS = Economic Committee on Health Care Products; CHIP = Children's Health Insurance Program; CIPM = Interministerial Commission for Pharmaceutical Prices; CHMP = Medicinal Products for Human Use; CMS = Centers for Medicare & Medicaid Services; CONITEC = National Commission for Incorporation of Technologies; CPP = Certificate of Pharmaceutical Product; DGFPS = Directorate General for Pharmacy and Health Care Products; DoD = Department of Defense; EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration; FDC = Federal Drug Commission; FOPH = Federal Office of Public Health; G-BA = Federal Joint Committee; GCPT = Therapeutics Positioning Group; GEPEC = Office of New Drugs Research and Clinical Trials; GKV-SV = National Association of Statutory Health Insurance Funds; INAME = National Institute of Drugs; IQWiG = Institute for Quality and Efficiency in Health Care; MEDSAFE = Medicines and Medical Devices Safety Authority; MHRA = Medicines and Healthcare Products Regulatory Agency; MoH = Ministry of Health/Minister of Health; NICE = National Institute for Health and Clinical Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; PBPA = Pharmaceutical Benefits Pricing Authority; pCODR = pan-Canadian Oncology Drug Review; PHARMAC = Pharmaceutical Management Agency; PRAC = Pharmacovigilance Risk Assessment Committee; PTAC = Pharmacology and Therapeutic Advisory Committee; SMC = Scottish Medicines Consortium; std. = standard; Swissmedic = Swiss Agency of Therapeutic Products; TC = Transparency Commission; TGA = Therapeutic Goods Administration; UNCAM = National Union of Health Insurance Funds; USA = United States of America; VA = Department of Veterans Affairs

No question there is room for improvement. The layers of approval section of the report will add further evidence that there are likely redundancies in the layers in both the approval and funding/reimbursement processes.

the USA, which had the highest levels of reimbursement.[35] The primary reason for rejection of an application for reimbursement was a lack of cost effectiveness; in New Zealand the primary reason was excessive cost.[35] Although the USA and Germany theoretically have the highest levels of reimbursement, their funding/reimbursement systems require providers and payers to pay for part of the therapies. Depending on the level of co-payment, it may mean that patients are unable to access all available therapies.

In the USA, results from the Commonwealth Fund 2012 Biennial Health Insurance survey showed that approximately 84 million people (almost half of all working-age adults) had no health insurance at some point or had out-of-pocket expenses that were so exorbitant they could be viewed as being underinsured.[2] The survey also showed that the number of Americans who were uninsured, underinsured or had gaps in their health coverage had increased steadily between 2003 and 2010 with the number of underinsured almost doubling from 16 million in 2003 to 29 million in 2010.[2] With the advent of the Affordable Care Act, we hope that access to health coverage will improve.

Australia's funding review process seems to be excessively complex (see flow chart on LC website at http://www.lymphomacoalition.org/global-report). Two committees review the clinical and cost effectiveness of a new therapy. Within these two review bodies (Pharmaceutical Benefits Advisory Committee [PBAC] and Pharmaceutical Benefits Pricing Authority [PBPA]), there are various subcommittees all seemingly examining the same information. And even when PBAC does provide a positive response, the government may not be in agreement. While it is rare for the government to reject a recommendation by PBAC, in February 2011, the government suspended eight medications and vaccines. "Although none of these medicines was for the treatment of cancer, the significant deviation from the routine process signalled a policy shift towards fiscal control rather than patient access."[13] The newly elected government in Australia has pledged that patients with blood cancer should have timely and affordable access to life-saving medications.[36] Time will tell if the new government is true to its word.

Under the 1978 Spanish Constitution, all citizens living in Spain have the right to universal access to public healthcare. Recently, however, Spain has undergone major changes to the way therapies are funded. For the first time, a co-payment for therapies delivered by hospital pharmacies will be required. In oncology, this applies to 32 drugs including imatinib (Gleevec, Glivec), nilotinib (Tasinga), dasatinib (Sprycel) and hydroxiurea (Hydrea, Droxia, Mylocel), which are widely used for the treatment of chronic myelogenous leukaemia.[25] What is of even greater concern is that every region in Spain can now re-evaluate or deny, for financial reasons, the use of a therapy that has already been approved by the EMA and the Spanish Ministry of Health. It would appear that Spain is adopting a system similar to Canada's, one that does not work to the benefit of the patient. In July 2013, Spain introduced measures to try and prevent the different regions from making their own funding decisions. It's unclear at this time how successful these measures will be.[37]

The 1998 Brazilian constitution guarantees universal access to healthcare for all citizens; however, not all medicines available in Brazil are included in the formulary. As a result of this situation, patients resort to legal action to force the government to provide the therapy. The number of lawsuits has increased from 3,200 in 2005 to 19,500 in 2010.[38] Lawsuits most frequently occur in oncology and rare diseases. Again, a patient has to fight to get a needed therapy rather than focusing on getting healthy.

Argentina has probably one of the more complicated funding systems in that most cases have to be negotiated to determine whether coverage will be provided. Coverage is provided by a mixture of public, semi-private and private funding bodies.[12] The process entails a patient receiving a diagnosis and being provided with a prescription. This may then require the doctor to contact the pharmaceutical representative who, in turn, contacts the payer to provide the payer with the information that the prescription fits the diagnosis. In breast cancer, coverage for 70 to 80 per cent of new cases had to be individually negotiated! While Argentinean law requires payers to cover all therapies, payers make every effort to delay providing such coverage. Again, another demonstration of making patients wait while payers decide how long payment can be either avoided or deferred. By law, patients with cancer including those with lymphomas are supposed to receive an approved therapy for their treatment at no cost to them, i.e., the cost of therapy is fully covered.[3] As well, patients can also receive a therapy that has been approved in another country, e.g., the USA, even if it is not approved in Argentina. The reality seems to be somewhat different and patients often have to resort to taking legal action to receive the required therapy.[3]

As treatments become more expensive, the funding/reimbursement process is only going to become more arduous and painstaking as governments and payers struggle to find ways to pay for these new therapies.

MOVING FORWARD

This report has shown there is not much to be satisfied about when it comes to getting therapies to patients with lymphomas in a timely and cost-effective manner. Bringing all players to the table to come up with solutions as to how to make therapies more affordable must be considered. Biologics or targeted therapies, which are becoming the mainstay of therapy in the treatment of lymphomas, are expensive. Consequently, there is a high risk that fewer of these therapies will be covered by government funding agencies or third-party payers resulting in fewer patients receiving appropriate therapy due to affordability. **The cycle – develop therapy, fight to have it approved and then fight to have it funded – cannot continue as it currently stands, it is not working.**

With a view to harmonising requirements, collaboration among countries could reduce the amount of time taken to issue marketing authorisations. Such collaboration would mean that data would not have to be scientifically re-assessed by each country's review body. The FDA and EMA have recognised the importance of collaboration to speed up development and availability of new drugs and have undertaken a number of combined initiatives. For example, they created a program to provide joint scientific advice to pharmaceutical companies that has often enabled makers of oncology products to use the same clinical trials to support approvals in both the USA and the EU.[10]

Based on the research undertaken for this report, the only country that appears to issue marketing authorisation at the regulatory level in a timely manner is the USA. While the USA may have more resources than some of the countries studied in this report, it might be of benefit to study how their system works.

As a Coalition, we call for:

- A round-table discussion with all parties (government, drug developers, patients, patient advocacy groups, physicians and private payers) to come up with solutions to make therapies more affordable for patients;
- Increasing the level of transparency at all levels of the process with all parties involved. It should be clear what is going on at every stage of the regulatory as well as funding/reimbursement review processes;
- Patients, patient advocacy groups as well as applicants to be included on committees throughout the decision-making process;
- Expectations of clinical trials to be communicated clearly at the start and then adhered to during the process. If changes are made to regulatory requirements part way through the trial, these changes should not affect reviews already underway.

As a lymphoma community, we can support patients and ensure they receive therapy in the most timely and cost-effective manner possible. To assist with this, consideration can be given to:

- Governments harmonising their processes and procedures;
- Governments reducing the cost of evaluating therapies;
- Challenging drug developers that state their goal or mission is to provide better therapies to patients to do so affordably;
- Drug developers collaborating on the development of biomarker testing that can be shared so patients receive the right drug at the right time.

Let's support the patient by being vigilant rather than complacent; never stop talking about lymphoma and the needs of patients with lymphoma. Keep the big picture in the background, don't let it become overwhelming; instead look at what your local area needs and what you can do to help patients with lymphoma. If you see a need bring it to the attention of the LC or the local lymphoma organisation.

In Phase III of LeIP, LC will make efforts to host a round table that includes all parties involved in the development of new therapies to come up with solutions as to how to make therapies more affordable and accessible to all patients.

In addition, LC will continue to:

- Monitor and report on the reimbursement and regulatory policy changes as they occur around the world and work with local communities to be a voice for patients;
- Develop as the global resource for lymphoma facts and statistics; include information on therapies that are funded/reimbursed;
- Develop ways in which healthcare professionals can be conduits between newly diagnosed patients and patient groups for support and lymphoma education;
- Ensure that clinical trial information is made more readily available to the patient community. This will be accomplished by updating the therapy access by country chart and adding information on clinical trials as it becomes available. It is also the intent of the Coalition to determine how this information can be made available in languages other than English;
- Work closely with drug developers to ensure that as the development and use of oral therapies becomes more prevalent for the treatment of lymphomas, patient needs are taken into account, e.g., provide patient education to deal with compliance issues, use of blister packs, etc.

If nothing else after reading this report card, think of one thing you can do to make a difference to patients with lymphomas in your country so they can receive therapies in a timely and cost-effective manner.

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CAUSES & RISK FACTORS OF LYMPHOMA
LATEST FINDINGS FROM INTERLYMPH CONSORTIUM 2013

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What is InterLymph?

The International Lymphoma Epidemiology Consortium (InterLymph) is an open scientific forum for epidemiologic research in non-Hodgkin lymphoma (NHL). Established in 2001, the Consortium is an international collaboration of scientists who undertake research projects that pool data across studies to better understand lymphoma risk factors. Although the main emphasis of the collaboration is epidemiology, InterLymph has expanded to include geneticists, pathologists, immunologists, clinicians and other scientists and now includes more than 100 members. InterLymph now consists of four working groups (immunology and infection, lifestyle and environment, pathology and survival, and genetics), and has evolved to include multiple large scale projects that operate across working groups. (http://epi.grants.cancer.gov/InterLymph/)

What are the goals of InterLymph?

The overarching goal of InterLymph is to identify patterns of commonality and heterogeneity in the etiology of NHL subtypes. This knowledge has implications for understanding biology, etiology, prevention and control of these malignancies. The Consortium aims to achieve this by addressing research questions that are difficult to answer in individual studies, by sharing data and biological samples. The Consortium has established a central data coordinating centre that is a repository of pooled, harmonized data from all participating studies. To date nearly 30 peer-reviewed manuscripts describing pooled InterLymph Consortium studies have been accepted for publication.

Latest findings from InterLymph

Several genetic risk factor studies were published in 2013. The first was led by Dr. Susan Slager from the Mayo Clinic (United States). Using the latest high-throughput technology to test the DNA of 3,100 individuals with chronic lymphocytic leukaemia/small lymphocytic lymphoma and 7,667 healthy controls, 10 common genetic variants at 10q23.31 (ACTA2/FAS), 18q21.33 (BCL2), 11p15.5 (C11orf21), 4q25 (LEF1), 2q33.1 (CASP10/CASP8), 9p21.3 (CDKN2B-AS1), 18q21.32 (PMAIP1), 15q15.1 (BMF), 2p22.2 (QPCT), and 2q13 (ACOXL) were identified to be associated with CLL/SLL. (Berndt S et al. Nat Gen. 2013). In the second study led by Dr. Alexandra Nieters from the University Medical Center of Freiburg (Germany) based on 5,633 B-cell NHL cases and 7,034 controls demonstrated that gene variations in the proapoptotic BCL2L11 gene were associated with B-cell NHL (Nieters et al., Blood 2001;120(23);4656-8). In the first gene-environment analysis of NHL risk factors, Dr. Todd Gibson of the U.S. National Cancer Institute found current smoking to be associated with a significant 30% increased risk of follicular lymphoma, but did not find that the associations were modulated by the NAT1 or 2 gene (Gibson TM et al. Cancer Causes Control 2013;24(1):125-34).

In a study of cigarette smoking and Hodgkin lymphoma (HL), Dr. Henrik Hjalgrim of the Statens Serum Institute (Denmark), evaluated data from 3,335 HL cases and 14,278 controls. Compared with never smokers, ever smokers had a modest 10% increased risk of HL, largely among mixed cellularity HL and EBV-positive HL among current smokers, while no risk increase was observed for nodular sclerosis and EBV-negative HL, supporting the notion of etiologic heterogeneity between HL subtypes. (Kamper-Jorgensen et al. Ann Oncol. 2013 24(9):2245-55).

Finally, Dr. Nicolaus Becker of the German Cancer Research Center (Germany) led a pooled analysis of self-reported history of infections and NHL risk. Based on data from 12,585 cases and 15,416 controls, there was little clear evidence of any association between NHL risk and infections. (Becker N et al. Int J Cancer. 2012 131;10:2342-8.)

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2013 LeIP Situation Analysis Report

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