Payers' Views on Long Acting Injectables

Potential To Create Payer Value

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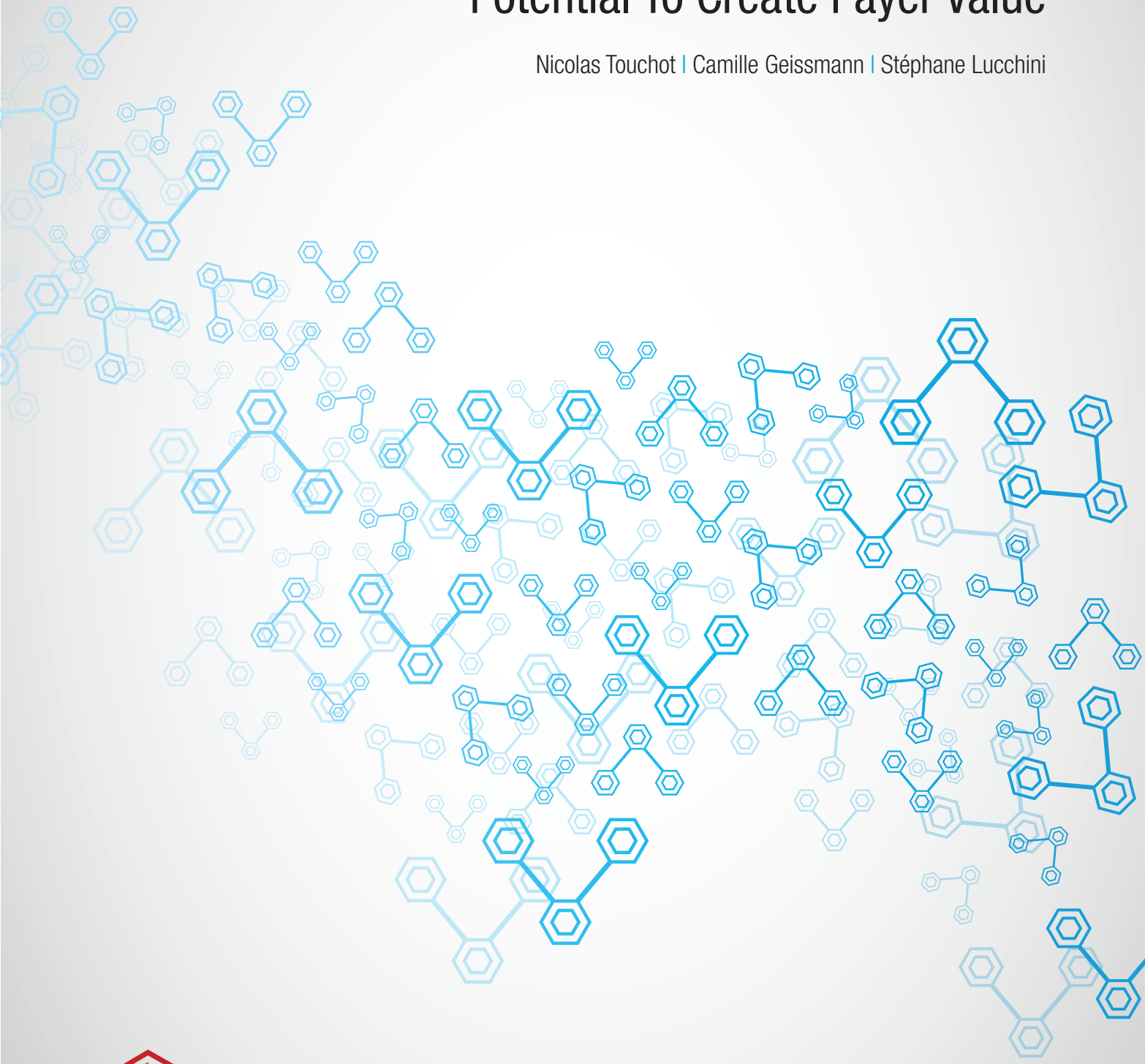


November, 2014

Payers' Views on Long Acting Injectables Potential To Create Payer Value

Payers are highly aware of the drawbacks of oral or injectable drug administration. Reformulation as Long Acting Injectables is seen as a powerful approach to improve the efficacy of multiple active pharmaceutical ingredients. These LAIs have the potential to create significant value for payers as well as for other key stakeholders in the health system in large chronic conditions such as diabetes or COPD as well as in smaller highly specialized indications such as transplantation. It can result from primary or secondary prevention of acute events, from a better control of chronic progressive diseases or infections, or from a variety / combination of other benefits created by increased adherence and efficacy and improved tolerability.

INTRODUCTION

Long Acting Injectables (LAIs) have been on the market for more than 20 years and have gained significant share in indications such as psychosis, acromegaly, alcohol addiction or endometriosis pain. The products, their benefits and the associated value are well known to payers and have been rewarded through positive reimbursement / coverage decisions and through price premiums.

However, so far the development of LAIs has often been impaired by limitations to the delivery system. This problem is being challenged by the development of novel approaches such as MedinCell's biodegradable polymer depot that allows formulation of a large number of active pharmaceutical ingredients into LAIs that provide highly favorable pharmacokinetic profiles, and are very safe and easy to use. This will lead to a new wave of LAIs with the potential to create value for all key stakeholders of the health system: patients, providers, payers and society.

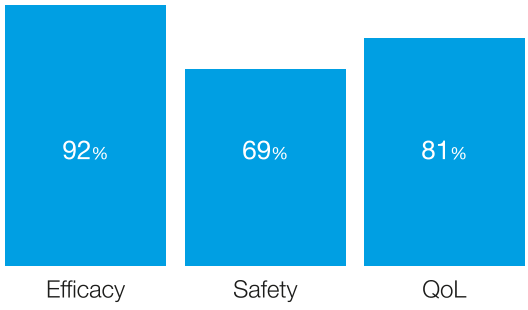
In this White Paper we explore payers' expectations from LAIs and their perception of the value that these novel LAIs could generate. We illustrate these beliefs through specific examples with the description of the value created. Weidentify potential Market Access hurdles for LAIs and offer approaches to overcome these hurdles.

Note: *This White paper does not list all indications identified by payers to be of interest for LAIs but simply specific examples as illustration of value. These examples do not predict feasibility of development of LAIs for the indications or molecules mentioned by payers.*

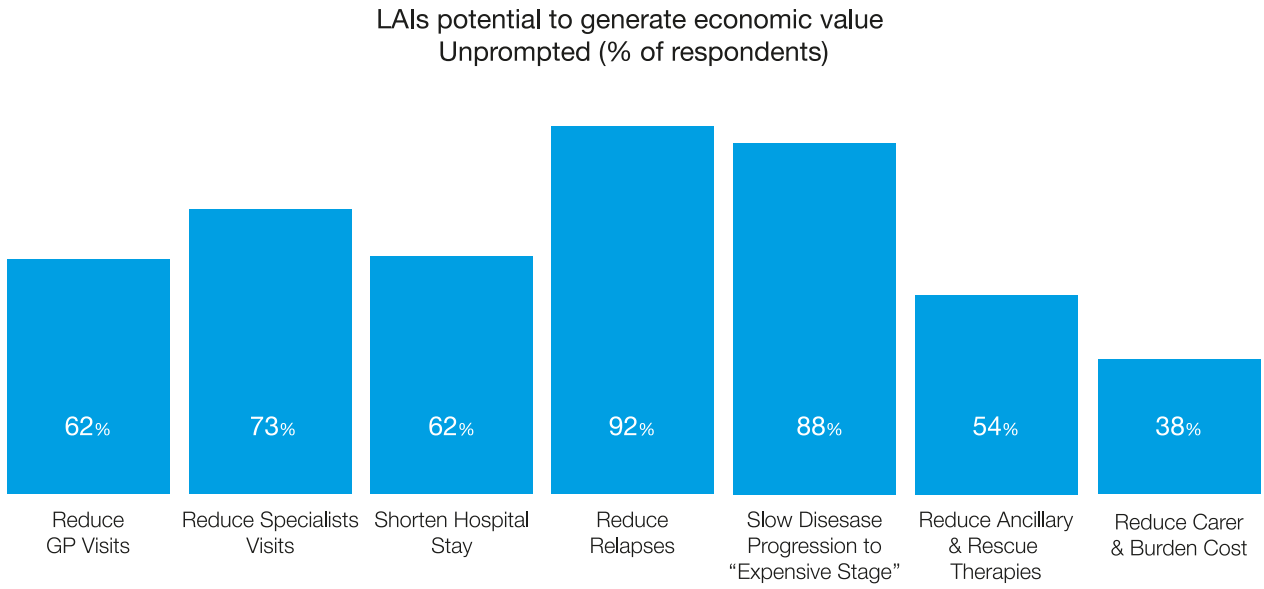
PAYERS' OVERALL VIEW OF LAIs' VALUE CREATION

There is general consensus amongst payers that LAIs can create value in multiple ways. The large majority of payers initially focus on clinical value. The key clinical value driver is efficacy but payers do not overlook the safety / tolerability, or the Quality of Life (QoL) elements. All three are often perceived to be related to each others, with improved tolerability leading to improved adherence and therefore efficacy, both contributing to improved QoL.

LAIs' potential to generate clinical value
Unprompted (% of respondents)



Payers also identify multiple ways by which LAIs can create economic value. As we will discuss in more details in this White Paper, payers believe that the two main potential drivers of economic value are the reduction in relapses and the slowing of the disease progression to "expensive stage".



Long acting antipsychotics are considered by payers to be the "poster child" of long acting injectable drugs. They illustrate the benefits: reduction of relapses and reduction of treatment costs while also illustrating some of the challenges, such as demonstration of benefits in a clinical trial setting and the need to target a well defined population most likely to benefit from LAIs.

But payers also mention that unfortunately, several other LAIs on the market, or coming to market have been evaluated against placebo, and fail to demonstrate the benefits and value of the new delivery mechanism and regimen. The words "long acting" do not create value by themselves, even in patient populations where convenience is important and adherence is known to be low. This value has to be demonstrated through undisputable evidence.

DETAILED FINDING FROM PAYER RESEARCH ON LAIs AND ASSOCIATED VALUE

ADHERENCE

Detailed description of three areas consistently mentioned by interviewees

Secondary prevention / reduction of hospital readmission

Improved control of chronic long-term diseases

Improved management of infectious diseases

Summary of other avenues to create payer value

Avoidance of rare but "high impact" events - Improve treatment of specific "challenging" patient populations - Improved efficacy - reduced burden of local administration - Primary prevention and initiation of therapy

IMPROVED SAFETY AND TOLERABILITY

BARRIERS AND CHALLENGES IN CREATING VALUE THROUGH LAIs

SPECIFIC BENEFITS OF MEDINCELL'S LAI TECHNOLOGY

ADHERENCE

The World Health Organization (WHO) defines adherence as the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from health care providers.

To date, measurement of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice. For this reason, medication adherence has been called the "next frontier in quality improvement" and is perceived by payers as an important part of outcomes research. One interviewee mentioned a 2003 report from WHO showing that adherence rates in developed countries was only 50%, but also stated that these rates are unlikely to have improved significantly since then.

Payers often use cardiovascular disease to illustrate the negative impact of poor adherence. Amongst other examples they mention:

- High adherence to antihypertensive medications is associated with higher odds of blood pressure control

compared with those with medium or low levels of adherence[1]

- An increase in proportion of days covered for statin medication is associated with a reduction in Low Density Lipoprotein (LDL) cholesterol[2]
- Non-adherence to statins in the year after hospitalization for myocardial infarction has been associated with increased risk of morbidity and mortality[3]
- In the chronic coronary artery disease setting, non-adherence to cardioprotective medications (β-blockers, statins, and/or angiotensin-converting enzyme inhibitors) is associated with an increase in the risks of cardiovascular morbidity and mortality[4]

Payers' concerns about adherence are not limited to cardiovascular disease and are growing across indications. Another area identified by many interviewees is cancer where historically patient-administered oral medications have played a relatively minor role compared with parenteral cytotoxic therapies. However, the growth of oral antineoplastic agents has now raised the issue of non-adherence in oncologic care. Interviewees express significant concerns at paying a high price for a limited increase in Overall Survival (OS) or in Progression Free Survival (PFS) if the data obtained in clinical trials cannot be replicated in real life due to poor adherence.

Other areas often mentioned by payers where adherence is major issue and affects outcome include diabetes, respiratory disorders, Central Nervous System (CNS) disorders, anti-infectives, transplantation, osteoporosis and ophthalmology thereby illustrating the broad potential for LAIs.

Payers believe that barriers to medication adherence are complex and varied. The only realistic way to improve adherence with existing products relies on multi-modal intervention, and can be very resource intensive for limited results. Payers mention several reasons to explain the difficulties in setting up effective adherence programs:

- Providers are poor predictors of adherence
- Providers are also poor evaluators of adherence
- Patients and their relatives do not understand the benefits of strict adherence. Their "health literacy" is often insufficient
- Physicians often fail to properly explain the benefits and adverse effects of medication(s)
- Electronic records of prescription refills are only available in a few countries, and are often not used as extensively as possible to identify patients with poor adherence
- Physicians often do not consider the financial burden to the patient in prescribing multiple therapies

"Unfortunately in today's environment we know that for most therapies adherence is going to be at best 60%. Any greater adherence should be considered as an improvement that increases the real life efficacy"

Payer, U.S.

In summary non-adherence or poor adherence is often perceived by payers as the base case. Perfect adherence is unrealistic.

This creates significant issues for both the clinical and the economic value of many drugs:

- The clinical value is based on randomized trials performed in a controlled environment where adherence is significantly higher than in real life
- Many Health Economic models assume perfect or clinical trial adherence and are therefore not representative of real-life situations

In this complex environment, payers see the use of LAIs as an easy approach to ensure adherence, requiring limited resources and with almost guaranteed efficacy. This is widely perceived by payers as likely to create significant value across multiple indications.

DETAILED DESCRIPTION OF THREE AREAS CONSISTENTLY MENTIONED BY INTERVIEWEES

Secondary prevention / reduction of hospital readmission

Hospital readmissions are a major cause of increasing medical costs and often are associated with poor quality of care. The consequences of hospital readmissions include the negative impact on patients' quality of life, decreased patient satisfaction with the hospital experience, and financial costs to the health care system. As a result, hospitals are under increasing pressure to reduce readmissions.

In the U.S., an analysis of 12,000 Medicare claims data showed that almost 20% of the Medicare beneficiaries who had been discharged from a hospital were re-hospitalized within 30 days, and 34%were re-hospitalized within 90 days[5]. In response to the increasing costs associated with readmissions, the Hospital Readmissions Reduction Program (HRRP) was implemented by the Center for Medicare & Medicaid Services (CMS) in October 2012. The program reduces Medicare payments to hospitals with high 30-day readmission rates for acute myocardial infarction, heart failure, and pneumonia. Using historical data, CMS determines, for each hospital in the Inpatient Prospective Payment System (IPPS), whether its readmission rates are higher than they should be given the hospital's case mix. The CMS model determines the targets by benchmarking hospitals against peers with a similar case mix[6]. Moving forward, new indications (chronic obstructive pulmonary disease - COPD and hip/knee arthroplasty) will be scrutinized and the penalty for excess readmissions will increase from a maximum of 1%(2013) to a maximum of 3% (in 2015). These percentages appear low, but are actually high relative to the average operating margin of U.S. hospitals, especially the not-for-profits that treat the majority of Medicare patients and show only about 2.5% profit margin[7]. In 2013 Medicare has

1. Bramley *et al*. J Manag Care Pharm. 2006; 12:239–245
2. Ho *et al*. Arch Intern Med. 2006; 166:1842–1847.
3. Rasmussen *et al*. JAMA. 2007;297:177–186
4. Gossec *et al*. Am J Med Sci. 2007;334:248 –254.
5. Jenks *et al*. N Engl J Med 2009;360:1418-28
6. Zhang *et al*. Northwestern University
7. The Advisory Board Company – Daily Briefing April 25,2014

collected almost $230 million in fines against 2,225 hospitals in every state but one.

These financial penalties implemented by Medicare are an attempt to stop the revolving door of hospitalizations. Private insurers from the U.S. indicate that they are likely to put in place similar programs to limit hospital readmissions.

In Europe, the scarcity of health resources and the increasing questions on the ability of public health systems to fund increasingly expensive drugs and procedures has also raised the question of unplanned hospital readmissions. In a study of a thousand patients aged 75 and older admitted to medical wards through emergency departments in nine French hospitals, 14.2% of inpatients returned through unplanned readmissions within 30 days[8].

In the UK, the National Health Service (NHS) saw a 50% increase in readmissions between 1999 and 2010. An average of 6.5% of patients were readmitted to hospitals within 30 days at a cost of about $2.4 billion (£1.6 billion) in 2011[9]. In 2010, The Department of Health introduced a new policy of non-payment for acute hospital readmissions. This policy means that local commissioners will not pay for any emergency readmissions to hospital within 30 days of discharge from a previous planned hospital stay.

Payers express a high interest in the use of LAIs for secondary prevention after an initial event leading to hospitalization. This is particularly true for indications that contribute the bulk of readmissions such as heart failure, psychosis, and COPD. This interest is reinforced by the fact that readmissions are often more costly than the initial admissions. In the Medicare analysis mentioned previously, the average hospital stay for re-hospitalized patients was 0.6 days (13.2%) longer than the stay for patients in the same Diagnosis-Related Group (DRG) who had not been hospitalized within the previous 6 months.

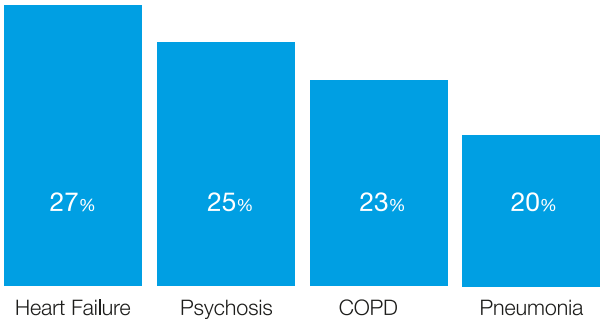
In the U.S. and in several other countries hospitals and health systems have make significant investments to reduce re-admissions "Discharge Planning" or "Transition Care" programs have been developed to reduce hospital readmission. However the cost effectiveness of such programs has yet to fully convince payers. A U.S. interviewee pointed to a real life evaluation by Baylor Medical center in Texas, showing a reduction of 48% of hospital readmission after heart failure, but also leading to a reduction of $225 on average on the hospital margin for each Medicare patient.

In the UK, the NHS has also developed guidelines for discharge planning through The Institute for Innovation and Improvement but the efficacy of those guidelines is considered limited by UK payers.

U.S. - Medical Conditions Associated with the Highest 30-Day Re-hospitalization Rates

(National Council for Behavioral Health 2014)

Percent Re-hospitalization at 30 Days for Each Indication



It is clear to payers that poor adherence to therapy is only one of the contributing factors to unplanned readmissions. However, it is an important factor, especially as hospitals attempt to achieve early discharge to reduce costs. The exact weight of poor adherence is difficult to evaluate, and certainly varies across conditions, but most interviewees estimate it to be around 25%. This makes it an interesting target with the potential to significantly impact the overall readmission rate

Taking cardiovascular as an example once again, payers point out that about one fourth of U.S. patients do not even fill their cardiac medications by day 7 following discharge after hospitalization for acute myocardial infarction[10]. For the same indication, another study showed that among patients discharged with prescriptions for aspirin, statin, and β-blockers, 34% of patients stopped at least 1 medication and 12% stopped all 3 medications within 1 month of hospital discharge[11].

So while payers do not expect LAIs to be a definitive solution to the question of hospital readmissions, they believe that significant progress can be made through the use of LAIs, especially if they are given in the hospital prior to discharge and if they provide 1-2 months of ensured adherence.

Achieving 100% adherence through LAIs is also perceived by payers as providing the opportunity to shift the focus and the investment of resources to other causes of hospital readmissions, such as improved follow-up by primary physicians or family training to support home care, and therefore to increase the return on investment associated to Discharge Planning programs.

Evidence generation and pricing – Secondary prevention / reduction of re-hospitalization

Payers consider the use of LAIs to reduce hospital readmission as a favorable positioning since it is possible to:

- Demonstrate a direct impact on outcomes with clinical trials of limited time and duration of follow-up
- Match the clinical benefit to economic benefits. For example for heart failure, payers estimate the cost of

8. Lanièce *et al*. Age and Ageing 2008; 37: 416–422
9. The Burrill Report, Hopsital Readmission in Europe
10. Jackevicius *et al*. Circulation.2008;117:1028 –1036.
11. Ho *et al*. Arch Intern Med. 2006; 166:1842–1847.

hospitalization at about $25,000. With a Number Needed to Treat (NNT) of about 20, this would justify an extra cost of about $1,200 per patient for the LAI. Since this price is considered out of the question for known molecules and for a 30-60 day treatment, payers believe that hospitals and health systems will capture the bulk of the economic benefits even with premium pricing for the LAI.

"If you have an indication with 25% re-hospitalization at 30 days and can reduce that to 20% through your LAI, you probably need a study with 500-600 patients only. We may ask you to provide 6 months data for safety, but this remains very manageable"

Payer, U.S. Pharmacy Director, Private Plan

Several interviewees indicate that in such indications they are even willing to accept comparison to a historical cohort of patients, if those are carefully constructed and matched to patients treated with LAIs.

One potential barrier identified by payers will be the need to cover the product from the hospital DRG in many countries. When there is a financial incentive to the hospital such as in the U.S. (Medicare) or in the UK, this is likely to be easily accepted, but when hospitals are reimbursed even in case of re-hospitalization, they may resist the extra cost and the transfer from a community drug budget to the hospital budget. However, this is not considered a major hurdle in most countries since the overall cost is expected to remain low compared to the DRG value.

Improved control of chronic long-term diseases

Payers do not need convincing that adherence in chronic conditions is low and has a very negative impact on long-term outcomes. This is even more acute in conditions that are asymptomatic and for which patients do not suffer from immediate symptom exacerbation in case of poor adherence. As a result, payers express a high interest in the use of LAIs for the management of chronic conditions. These conditions represent 65-70% of health care costs and non-adherence has significant clinical and economic impact. In the U.S., the total direct national cost of non-adherence for only three indications: diabetes, hypertension, and dyslipidemia, was estimated at $105.8 billion, or an average of $453 per adult, in 2010[12].

Payers separate chronic conditions in two main categories:

- Those where disease progression leads to a significant increase in clinical and economic burden such as diabetes, chronic kidney disease or glaucoma
- Those where exacerbation regularly leads to hospitalization, such as COPD, asthma or epilepsy

LAIs are perceived by payers to be attractive for both of these broad categories.

Within chronic indications, payers do not expect the full population to be a target for LAIs, but believe that it is possible to identify a population of patients with poor adherence, or at risk of rapid disease progression. In many health systems, prescriptions for chronic diseases are for 90 days. Payers believe that this provides an opportunity to define patients who are most likely to benefit from LAIs through:

- Use of electronic prescription refill records in countries where this is possible
- Failure to achieve target on specific parameters without clearly identified reasons, which could suggest that the real reason is poor adherence

Payers often focus on a few indications amongst which:

Type 2 Diabetes (T2DM)

All payers identify diabetes as an indication where poor adherence leads to poor control of the disease and therefore impaired outcomes. There is consensus that adherence to oral therapies for T2DM is around 60-65%. There is also consensus that low adherence is an important cause of increased morbidity and mortality[13]. Furthermore, it has been estimated that increases in medication adherence of only 20% could reduce total health care spending by $1,074 per year for every person with diabetes[14].

LAIs are perceived as a good approach to increase the number of patients for whom glycated haemoglobin (HbA1c) is maintained at (or brought to) target. The benefits would be a reduction in the long-term risks of retinopathy, neuropathy or nephropathy, along with a reduction in the risk of cardiovascular (CV) events.

Payers believe that LAIs could be integrated into Disease Management (DM) programs for T2DM. Initial experiences with DM programs 15-20 years ago were often disappointing for payers, producing mixed results. However more recent DM programs have yielded better results. In Germany, a disease management program for diabetes has lowered the overall cost of care by 13%. Payers believe that LAIs could be easy to integrate into disease management programs, simplifying therapy for both provider and patient and allowing the resources of the program to be focused on other elements.

In the U.S., payers also suggested the integration of LAIs into employer-sponsored Medication Therapy Management (MTM). These programs include personalized medication review, creation of a medication action plan, and clinical and lifestyle interventions, with all these components aiming to lead to target clinical goal attainment by patients. They have been shown to be effective in reducing physician visits as well as emergency room and inpatient visits for diabetic patients[15]. Payers suggested that employers would be highly interested in ensuring compliance in order to reduce the cost burden of

12. Nasseh *et al*. m J Pharm Benefits. 2012;4(2):e41-e47

13. Asche *et al*. Clin Ther.2011;33(1):74–109
14. Sokol *et al*. Med Care. 2005; 43(6):521–530
15. Pinto *et al*. Clinico Economics and Outcomes Research 2013;5:153–159

the disease to companies. In 2007, diabetes was found to be the cause of 15 million workdays lost to employers[16].

Chronic Kidney Disease (CKD)

Payers often mention CKD as an attractive target for LAIs, as compliance with ACE inhibitors and ARBs is perceived to be low and as proteinuria control is perceived to be directly associated with irreversible loss of kidney function. This is then followed by progression toward End Stage Renal Disease (ESRD), leading to the very high cost associated with Renal Replacement Therapy and to the increased risk of CV events associated with progressive kidney disease. Payers express a strong interest in improved adherence to ACEis (or ARBs) that could lead to a demonstrated improvement in the control of proteinuria / albuminuria.

Hypertension

Not surprisingly, hypertension is also high on the list of indications where LAIs could provide significant value. Despite the availability of many anti-hypertensive drugs, payers point out that only about 70% of patients being treated have their blood pressure well controlled. They believe that poor adherence is a major reason for failure in the remaining 30% of treated patients. The expected benefits are very similar to those for diabetes with a clear surrogate endpoint: control of blood pressure to target that is associated with improved long-term outcomes, including cardiovascular and kidney diseases.

COPD and Asthma

Payers acknowledge that their interest in the use of LAIs for indications such as Asthma and COPD may seem surprising, as these indications are mostly treated by inhaled therapies. However these indications also illustrate how a LAI could generate interest for oral drugs that have proven benefits but are not as broadly used as they could be such as Montelukast.

Payers point out that many patients are poorly compliant with their inhaled therapies (LAMA, MABA, ICS or combinations), that is when they know how to use their inhalers properly. There is therefore an interest in a background therapy with high compliance that could reduce the rate of exacerbation. This therapy would not replace the use of inhaled corticosteroids or β agonists but would complement an inhaled therapy, potentially allowing the patient to be managed by a monotherapy instead of requiring the more expensive combination inhalers, and reducing the risk of exacerbations.

LAIs' potential to improve performance indicators in chronic conditions (mostly U.S.)

In the U.S., the Medicare 5 star system has now introduced performance measurement for large chronic indications. Under this initiative, each MA contract receives a quality star rating from 1 to 5, in half-star increments. Plans receive a bonus payment based on their quality star rating equal to a percentage increase in the plan-wide benchmark payment rate. This bonus payment can reach 5%. One of the five domains contributing to the rating is the management of chronic long-term conditions, including diabetes and hypertension. Payers therefore see LAIs as a potential route to improve their performance with respect to these long-term indications, thereby increasing revenues for the plan and helping offsetting some of the premium associated with LAIs.

Outside the U.S., performance measurement are not formally established as of today, but are being developed. In the UK, a large series of outcome indicators has been developed by NHS and NICE to evaluate the performance of Clinical Commissioning Groups (CCGs). These indicators are not tied to financial incentives yet, but allow CCGs to compare themselves to the country average. Payers for several other countries indicate that performance indicators are likely to be increasingly developed and used for large chronic conditions.

LAIs' potential to reduce "Therapy Cycling" and discontinuation in chronic conditions

There are indications where the combination of poor tolerability and uncertain efficacy leads to treatment discontinuation or demands by patients to switch therapy. An indication with very high discontinuation identified by payers is Lower Urinary Tract Symptoms (LUTS) or Overactive Bladder (OAB). Payers mention discontinuations in excess of 50% for anticholinergic medications. While payers believe that continuous therapy is not always necessary to maintain efficacy, they also believe that many patients are unsatisfied with current agents and return to their provider to seek a novel therapy. This results in a combination of waste of drugs that are often unused, and waste of health resources as physicians cycle through therapies to accommodate the patient. LAIs are perceived as a way to increase both tolerability and efficacy and reduce the waste of health resources.

LAIs' potential to deliver important complements in the management of chronic conditions

Payers' interest in using LAIs for chronic diseases is not limited to drugs. Payers also see a potential in using LAIs to provide supplemental elements such as calcium or Vitamin D if daily intake is inadequate. For example Vitamin D deficiency in elderly patients has been associated with a significant increase in the risk of falling and increased susceptibility to fractures. Primary treatment is oral supplementation but elderly patients are prone to forget their pills, thereby limiting the efficacy of the supplementation regimen.

LAIs' potential to "rehabilitate" effective drugs with high pill burden for chronic conditions

Payers acknowledge that in chronic diseases, there is a justifiable preference for once-a-day products, especially if the patient is on poly-therapies. They also recognize the

16. American Diabetes Association. Direct and indirect costs of diabetes in the United States, 2009

direct relationship between dosing frequency and adherence, with once daily regimens showing higher adherence than 2-times, 3-times or 4-times per day regimens[17].

> *"There are probably many good drugs that are not prescribed simply because the current regimen is complex, and that could represent very good value for money if they were brought back as a long acting injectable. This may not be highly innovative, but it is a practical way to answer patient needs"*
>
> Payer, Italy, Regional Health Authority

As a result, payers see a potential for LAIs to be used for drugs that, when taken orally, require high dosing frequency. Such drugs have often fallen out of favor with physicians and patients, not because of poor clinical performance or poor tolerability but simply because of poor convenience. Their benefits may also have been underestimated in clinical trials due to poor adherence in the trial setting itself. By eliminating the convenience impediment, LAIs could renew interest in these drugs and allow the harvesting their full efficacy potential.

Evidence generation and pricing – Improved control of chronic diseases

In long-term chronic conditions, payers understand that it will be very difficult, if not impossible, to demonstrate an impact on long-term outcomes. This would require thousands of patients and several years and is not a viable economic proposition. As a result, payers show a strong willingness to accept an impact on a surrogate endpoint that has been linked to the long-term outcomes, such as HbA1c, proteinuria, blood pressure. Payers comment that if the surrogate marker is accepted by regulators and has been accepted by health technology assessment bodies in the evaluation of the originator molecule, there is no reason why they should not be accepted for LAIs. In addition, since the surrogate endpoints are being used by health authorities for performance measurement, there is logic in accepting them as a demonstration of benefits for LAIs.

However payers caution against the fact that the benefits of LAIs may be minimized in a clinical trial setting since adherence in the control arm will be higher than in real life. This would be the case for any indication but is perceived by payers to be even more relevant in long-term chronic indications where adherence probably decreases over time. The challenge will then be to convince payers of the reality of improved control in real life, if only a trend can be shown during clinical development.

As a result, payers are open to pragmatic trial designs for LAIs to maximize applicability. Payers also expect value dossiers to include a large body of historical data on real-life adherence (or lack thereof), helping to support the "story" for LAIs. Whether these real-life data will be accepted or not depends on the quality of the data collection and analysis. Payers perceive this as a challenge, but one that can be overcome.

> *"In real life you will compare 100% adherence with LAI to 60% adherence with the oral. In your trial you will still compare 100% adherence with LAI but to maybe 80% adherence with the oral. We understand that, but the fact that we understand does not explain how you will make that be taken into consideration in our formal benefit assessment process"*
>
> Payer, Germany Formulary Advisor for a Large Sickness Fund

In terms of pricing, the case for LAIs in the control of chronic disease will often rely on the benefits of maintaining patients to target. It will be very difficult to support pricing through health economic models, and when developed, payers indicate that they will consider those with caution, running their own scenario analysis and challenging assumptions on disease progression and occurrence of events. **Nevertheless prices in the range of the branded originator prior to genericization or even a small (20-30%) premium are perceived as likely with strong data.**

Supporting the price of products that reduce the risk of exacerbation is perceived to be easier, as the occurrence of events is the main measure of efficacy. Again in these cases, payers believe that prices in the range of the branded originator or even a small (20-30%) premium are perceived as likely with strong data.

Improved management of infectious diseases

Another area identified by payers as high interest is that of infective diseases, both for bacterial and viral infections. In a meta-analysis including nearly 30,000 patients receiving antibiotics in the outpatient setting, an overall non-compliance rate of 40% was observed[18]. In viral infections, payers point to studies showing that poor adherence leads to increased viral load and increased risk of viral breakthrough. For example in a U.S. series of patients with chronic Hepatitis B treated with nucleoside analogues, patients maintaining full adherence over time only showed a 2.2% rate of viral breakthrough, while this rate increased to almost 19% in patients showing poor adherence[19]. Similar data have been shown in other countries.

This is true also for Hepatitis C where adherence of >85% to pegylated interferon and ribavirin treatment is associated with increased Hepatitis C viral suppression. In an indication that is becoming overly expensive with the recent sofosbuvir launch, and where the patient population is perceived as having very low adherence, payers express a high interest in investigating how "older" drugs could demonstrate improved efficacy through LAIs.

17. Coleman *et al*. J Manag Care Pharm. 2012;18(7):527-39

18. Kardas *et al*. Int J Antimicrob Agents. 2005;26:106-113
19. *Chotiyaputta et al*. Journal of Viral Hepatitis, 2012, 19, 205–212

Payers also expressed an interest in less serious infections where patients often discontinue therapy upon symptom relief, even though continuing treatment to its completion is necessary for a complete elimination of the infection. Payers mentioned antibiotics where the normal course maybe be 7-10 days and where treatment is often discontinued after 4-5 days, leading to relapse, new visits to the prescriber and new prescriptions in these cases, a long acting injectable providing treatment for the required amount of time is perceived as creating value.

Payers also express an interest in the use of LAIs in prophylaxis for infectious diseases. For example the rate of adherence to long-term antibiotic treatment for recurrent Urinary Tract Infections (UTIs) is high, which leads to preventable infections and resulting renal scarring.

Several U.S. payers quote Tuberculosis (TB) as a good example of the relationship between high adherence and efficacy of anti-infectives in indications requiring long therapies (often >6 months). When U.S. cities introduced Directly Observed Therapy (DOT) for TB, the incidence of TB declined sharply. However DOT did not always yield good results in developing countries, one of the reasons often quoted being the difficulty and the cost to implement full DOT programs. Family observation is perceived as possible but also very unreliable. Payers see LAIs as a potentially cheaper and more effective alternative to ensure adherence. Drug resistant TB is becoming an increasing burden in many countries and payers also express a significant interest in the impact that a LAIs could have on resistance development for TB.

> *"Despite many progress over the last 15 years TB is still highly prevalent in Brazil and the treatment success rate is about 55%. If you can use a LAI to increase that rate to 70 or 75% that will be a great public health advance"*
>
> Payer, Brazil, Health State Department

Evidence generation and pricing - Improved management of infectious diseases

To demonstrate the benefits of LAIs in bacterial infections, payers would like to see at least non-inferiority in time to clinical and bacterial cure, plus superiority in the reduction in relapse.

In viral infections, increased sustained virological response and reduction in viral breakthrough would be perceived as evidence of superiority for LAIs.

In indications such as TB, payers indicated that there would be no need to demonstrate an improvement in long-term outcomes prior to launch of the product. A LAI will fit perfectly within both country programs and WHO efforts. The long-term benefits could be demonstrated at a later stage.

In both indications, payers believe that pricing and reimbursement will be relatively easy to justify though a combination of clinical and economic benefits. A price premium to the branded product is perceived as very realistic to expect.

Payers also believe that LAIs can be used to avoid expensive anti-viral agents. If more patients can be treated with cheaper products or with less complex combination therapies, the case can be made against expensive antivirals.

SUMMARY OF OTHER AVENUES TO CREATE PAYER VALUE

Payers do not limit their interest for LAIs to indications where adherence is low. They also express interest for indications where adherence is high (relative to other indications) but where the consequences of poor adherence or of missed doses can be significant.

High adherence / high consequences for non-adherent patients: Example of transplant

An area identified by many interviewees is that of transplantation. Although immunosuppressive therapy after organ transplantation is paramount for long-term outcomes, patients do not comply with their immunosuppressive treatment as much as might be expected. In a French study of patients having undergone kidney or liver transplantations, the majority of patients described themselves as poor compliers[20]. In another trial in The Netherlands, patients with kidney transplant reporting poor adherence had a lower 2-year graft survival compared to the adherent group (84% *vs.* 98%)[21].

This non-compliance in transplant patients is perceived very negatively by payers as it has a very negative impact both clinically and economically:

- Economically, as the direct and indirect costs of graft failure is very high
- Clinically, as the shortage of transplants means that another patients (a more adherent one) could have benefited instead

Payers consider that failure due to poor adherence is simply unacceptable and reducing graft failure through LAIs would create clear value. Payers indicate that they will be happy to provide coverage.

Significant impact of missed doses

An example of value creation identified by payers in indications where missed doses can have a strong negative impact is epilepsy. In that indication, non-adherence to Anti Epileptic Drugs (AEDs) may lead to a loss of seizure control. In a large survey of epileptic patients and neurologists treating epilepsy patients, non-adherence was found to be associated with reduced seizure control, lowered quality of life, decreased productivity, seizure-related job loss, and seizure-related motor vehicle accidents[22].

Payers also identified anti-coagulants as a potential target, as the impact of sub-optimal coagulation can be quite dramatic. However a potential barrier here is the need to reverse

20. Dharancy *et al*. Clin Transplant. 2012 May-Jun;26(3):E293
21. Tielen *et al.* Journal of Transplantation Volume 2014
22. Hovinga *et al*. Epilepsy & Behavior 13 (2008) 316–322

anticoagulation in case of surgery, and LAIs may be at a disadvantage.

However, in these indications, payers also believe that the consequences of missed doses differ across products. They express more interest in using LAIs for agents with shorter half-lives.

Treatment of specific "challenging" patient populations

The success achieved with anti-psychotics leads payers to believe that similar value creation can be replicated in other groups of patients that are considered difficult to treat because of CNS disorders or other reasons.

Dementia and Alzheimer's disease would be considered as perfect indications for LAIs but here the issue is that no drug seems to provide a real benefit. Payers also consider bipolar disorder patients as very likely to benefit from LAIs. Mood stabilizers (Lithium, valproic acid or carbamazepine) could be delivered by LAIs, while other therapies that require more regular adjustments in dosing could be delivered orally. Attention Deficit Hyperactivity Disorder is also mentioned as a potential target.

Interestingly, in patients with CNS disorders, payers believe that LAIs can provide value in both non-institutionalized and institutionalized patients:

- In non-institutionalized patients, the benefit is simply to enhance adherence and to prevent or delay institutionalization and the associated cost and impact on patient QoL
- In institutionalized patients, payers point out the very significant nursing time that is expended to make sure that patients take their medicine as planned, or to convince / force them to do so. The use of LAIs could significantly reduce this nursing time, allowing either reduce staff (in some countries) or to reallocate staff to other tasks

All therapies for addiction are also perceived by payers to be interesting candidates for LAIs, as adherence is often a major issue and cause for failure. Naltrexone is already available as a long acting injection and is perceived by payers as a valuable product. Similar formulations could be developed for acamprosate or other molecules for addiction. Payers also mention potential value in androgen deprivation therapies for sexual offenders.

Improved efficacy / reduced burden of local administration through LAIs

Payers express a strong interest in the use of LAIs in indications where drug yield to the desired location is either very low or very unpredictable. Ophthalmology is perceived as a good indication, one where biodegradable implants have already proven their value with products such as Ozurdex. Payers are interested by the use of LAIs for both front of the eye and back of the eye diseases.

In the back of the eye, sustained delivery of anti-VGEFs could increase efficacy, while decreasing the burden of repeated intra-vitreal injections for the patient and the ophthalmologist.

In front of the eye, glaucoma is often identified as a very attractive ophthalmic condition for LAIs, as there is a clear marker of efficacy and conversely of risk of disease progression through Intra Ocular Pressure (IOP). Compliance with eye drops is perceived to be very low and surgical procedures are expensive. An LAI that improves control of IOP and therefore the risk of disease progression and loss of vision is perceived by payers as providing clear value.

Intra-articular delivery also generates interest as patients with joint pain consume significant health resources. In several countries expensive injectable products such as hyaluronic acids are not covered and therefore do not impact payer budgets. However, many patients ultimately progress to total joint replacement, especially in the case of severe knee pain, leading to high direct and indirect costs. Payers express little interest for LAIs that would simply show an incremental improvement in pain control but would be highly receptive to a LAI that improves functionality / activities of daily living over a sustained period and reduces the risk of surgery.

Beyond these two examples, payers are receptive to local use of long acting products and express significant interest in delivery of drugs that do not cross the blood brain barrier (with questions around brain pressure created by the implant), as well as for products that require high local concentration over the long term, such as factors for neuro-protection or neuro-regeneration.

Primary prevention through LAIs

While payers focus more on secondary prevention than on primary prevention, they do not discard LAIs potential to create value for primary prevention, especially when used with products that may offer a relatively broad range of benefits. An example often mentioned is Raloxifene in post-menopausal women, which has been shown to prevent osteoporosis, while reducing the incidence of breast cancer. In such an indication the overall potential benefit is perceived by payers to justify the attempt to achieve full adherence through LAIs.

Improving Initiation of Therapy Through LAIs

Another area identified by payers as a potential value driver for LAIs is initiation of therapy. In the U.S., payers point out that about 20-25% of patients do not even fill the initial prescription, despite having proper insurance coverage. There are many reasons for this low "primary adherence", including fear of medication, misunderstanding of regimen, or patients not believing in the benefits of therapy. However without "primary adherence", then all questions about patients taking medication and continuing medication become irrelevant.

U.S. payers such as Kaiser Permanente have initiated automated outreach programs to call on patients that do not fill their prescription within 1-2 days of it being written. These programs start with an automated phone call and, if unsuccessful, continue with a letter. While these programs reduce by about 50% the number of patients not filling their

existing prescription, there is still a sizable number failing "primary adherence".

Payers see the use of LAIs at a physician practice as a useful tool to ensure primary adherence, with the expectation that patients who have initiated therapy will then be likely to continue.

> *"People always think of adherence as not continuing therapy, but patients often do not start. At least with the LAI you can ensure that the patient starts and continues for a few months"*
>
> Payer, U.S. Blue Cross Blue Shield

IMPROVED SAFETY AND TOLERABILITY

Payers understand the concept of improving safety and tolerability through a more regular PK concentration. This concept is known to them and has been supported by data on a few products. One example mentioned is tamsulosin Oral Controlled Absorption System (OCAS) for which a "smoothed" PK profile with more consistent release over 24h improves the efficacy / safety ratio compared to tamsulosin MR[23]. Another example often quoted by interviewees is that of extended-release metformin, that is often better tolerated than the immediate release form, especially in patients who have demonstrated Gastro Intestinal (GI) intolerance to the IR formulation.

However payers believe that examples of true value creation through improvement in tolerability are rare. Several interviewees mentioned the example of NSAIDs. They acknowledge that CV and renal toxicities, in addition to the more prevalent GI toxicity appear to be related to peaks of plasma concentration. They also recognize that these complications can lead to significant cost and use of health resources. But they also warn that demonstrating a long-term benefit associated with a reduction in peaks in serum concentration is virtually impossible.

As a result, payers recognize the importance of improved tolerability through LAIs but believe that these benefits will mostly contribute to improved tolerance and therefore to improved efficacy.

Nevertheless payers still recognize opportunities to provide value through improved delivery systems, including LAIs. U.S. payers mentioned the recent developments around Benicar (Olmesartan). The product is considered to have high efficacy in achieving control of blood pressure and high rates of goal attainment. However it has also recently been linked to enteropathy leading to severe diarrhea and substantial weight loss, which has caused the FDA to change the drug label to include these intestinal problems. Several payers believe that drugs facing this type of problem could benefit from being reformulated as LAIs to eliminate or strongly reduce the GI side effects. Such a rationale could be applied to whole classes of products such as cholinesterase inhibitors.

In creating value through improved tolerability, payers are also interested in simplifying the use of drugs that are inexpensive but perceived as difficult to use, especially when the next step in therapy is a highly expensive product. An example of such use mentioned during interviews is Methotrexate (MTX) and anti–TNFs for psoriasis. Several payers believe that MTX has high efficacy but is limited by associated tolerability concerns and the need to carefully monitor patients. A LAI formulation of MTX that would facilitate its use, and therefore delay the switch to anti-TNFs, would be perceived by payers as providing significant value.

> *"If you can keep the patient longer on a relatively cheap drug and avoid the progression to a much more expensive drug without compromising efficacy and safety you create direct and immediate economic value"*
>
> Payer, UK NHS Procurement

A tolerability benefit that payers point out should not be overlooked is also the timing of administration. With oral products there is a risk that patients take doses too close to each other thereby creating toxicity. This is something that is perceived by payers as very difficult to avoid despite patient education. The use of LAIs allows avoiding this toxicity due to poor "timing adherence".

BARRIERS AND CHALLENGES IN CREATING VALUE THROUGH LAIs

Despite the very strong interest expressed by payers in LAIs there are challenges, some of which have already been identified during the earlier review of positionings / indications.

Challenges in demonstrating evidence

Looking again at the example of schizophrenia, there is a debate whether LAIs truly reduce relapses and hospitalization. The comparative effectiveness of antipsychotic formulations is sensitive to research design. In a large literature review, depot formulations displayed significant advantages in non-randomized observational studies, whereas in randomized controlled trials, no difference was observed[24].

As mentioned previously, payers recognize the difficulty in representing real life gain in a clinical trial setting. In the meantime, they clearly express that, except in some specific indications such as tuberculosis, the onus of demonstrating the benefits of LAIs falls on the companies developing these products. **To reconcile these two statements, payers express a willingness to accept data coming from non-randomized studies, such as historical cohorts, open trials or registries**. However they also stress that evidence not derived from RCTs should be of very high quality, otherwise it will not be taken into account in benefit assessment.

23. Chapple *et al*. European Urology Supplements 4 (2005) 33–44

24. Kirson *et al*. J Clin Psychiatry 2013 ; 74(6):568-575

Another question often raised is whether continuous plasma concentration is actually better than the peaks and valleys observed with oral agents. While it sounds intuitive to payers, they are not convinced that it is always the case.

Payers will evaluate LAIs as any new product, with a focus on demonstrated patient-relevant benefits. Pharmacokinetic data are considered to be necessary but are considered by payers as proof of concept only, demonstrating the long-term delivery of the active pharmaceutical ingredient but nothing more.

As a result many payers foresee evidence generation in two phases: a first phase demonstrating non-inferiority to oral therapies for regulatory approval, and potentially showing a trend toward superiority, followed by a second wave of evidence generation demonstrating benefits in pragmatic trials.

Challenges in demonstrating economic benefits

The challenges in demonstrating economic benefits are perceived by payers to be even higher than in demonstrating clinical benefits. In many indications, payers believe that it will not be possible to clearly demonstrate economic benefits, even though those may appear logical or may be inferred.

Again payers understand these facts and will not demand such a demonstration of economic benefits for indications such as control of diabetes or of CKD, or for improved control of infectious diseases. However they nevertheless value a clear demonstration of health economic benefits in the positionings / indications where this is perceived as possible, such as short-term secondary prevention after an acute event or prevention of expensive events such as transplant failure.

Challenges in selecting patients for LAIs

Selecting the right patients for LAIs is perceived by payers to be a challenge. Payers believe that it cannot simply be left to physicians to select patients likely to benefit from LAIs. They also admit that if it is left to them, they will probably be restrictive in selecting sub-populations. As a result they will look toward the industry to provide them with the data allowing them to segment target populations and to make rationale decisions. Failing to do that will likely result in restrictions that will deny the benefits of LAIs to significant groups of patients that could have benefited from them. In the U.S., this is likely to translate into unfavorable tier decisions and requirements for prior authorization. In Europe it would translate into limitation of reimbursement or coverage to specific subgroups.

Challenges for patients treated by polytherapies

Many chronic conditions require polytherapies, with patients often combining 3+ active principles and a large number of pills per day. Several payers express a concern that using an LAI for just one active principle may have a low benefit, if it does not improves adherence to the other components of the therapy.

However payers do not consider this as a definitive barrier, as long as improved efficacy of the most important element of therapy is demonstrated. Payers even believe that there will be an indirect effect of using an LAI for one of the products, reducing the overall pill burden to the patient and improving adherence to the remaining oral therapies.

Patient education leads to higher long-term return on investment than LAIs

While payers see LAIs as a very good short-term solution to adherence, they also consider that in the long-term, improving patient "health literacy" and therefore increasing patient's responsibility in managing his/her disease is likely to have a higher return on investment. Patient education has a long-lasting impact, and affect not just adherence to drug treatment but also adherence to lifestyle modifications, diet adjustments, exercise programs… So payers warn that LAIs should not eliminate the needs for other efforts to improve patient responsibilization in disease management.

Challenges in co-pays or out-of-pocket payments

In countries with significant co-pays or out-of-pocket payments, payers fear that the likely premium associated with LAIs could be a barrier to patient access to LAIs. That may be even truer in select cases in the U.S. where generics are very inexpensive and may be cheaper over-the-counter than the co-pay required through prescription. Payers will be looking for companies developing LAIs to also develop the patient access programs and pricing strategies permitting broad access to all patients likely to benefit from the products.

SPECIFIC BENEFITS OF MEDINCELL'S LAI TECHNOLOGY

Payers perceive MedinCell's biodegradable polymer depot to be a differentiated approach for the development of LAIs. The technology has the potential to bring several advantages that enhance the value create by the use of LAIs, including:

Benefits of self-administration (when possible)

The potential for self-administration is perceived by payers as a clear benefit especially in the U.S. where long-term injectables can be classified as a "medical benefit" and not as a "pharmaceutical benefit", including by Medicare (through part B). By comparison, many health plans cover self-injectables under the outpatient prescription drug benefit, just as they cover any other self-administered oral, topical, or inhaled agent.

Administration reimbursed as a medical benefit includes both a drug reimbursement component and an administration reimbursement component and is usually more expensive to the plan due to different contracting processes. It can also be more expensive to the patient as a medical benefit product usually includes a high deductible and a co-insurance after the deductible is met.

EU payers apply the same reasoning to prefer products that can be self-injected by patients.

Benefits of potential removal of the depot

Payers also believe they there are potential specific benefits to the use of a sub Q gel-based implant. While they understand that the objective is not to adjust therapy by removing the implant, they are reassured by the fact that in case of severe adverse reaction, or strong medical need, a minor surgical procedure allows removal or the residual "lump" of gel.

PAYERS' VIEWS ON LAI PRICING?

Payers believe that LAIs will be priced based on the demonstrated benefits, and not based on the price of the active pharmaceutical, even if it is generic. Assuming that LAIs can provide the expected benefits, they are highly confident that LAIs can achieve a price at least equivalent to the branded product and in many cases achieve premium pricing compared to that branded product, especially since many branded products now have prices close to that of their generic.

There are significant expectations that LAIs can demonstrate positive health economics. For example, in indications where re-hospitalization is prevented, a 15-20% relative decrease in re-hospitalization resulting from a month or two of therapy with a slightly more expensive drug is perceived to be likely to result in overall savings to the health system, leaving room to capture part of these savings through enhanced pricing. In such indications, the number needed to treat is perceived to be low and very favorable to support the use of LAIs.

In specific countries such as Germany, most LAIs will escape formal review (AMNOG) since the active principle is already known. LAIs will be priced freely and will be covered by law. Market Access will be self limited by physicians who will want to protect themselves in case of an "efficiency" audit, should they overshoot their drug budget. In that environment, it will be important to provide a clear justification of benefits in order to allow physicians to use LAIs without anxiety.

CONCLUSION

Payers are highly aware of the drawbacks of oral or injectable drug administration in countless indications and patient groups. Despite significant investments to increase adherence, the outcomes of many therapies are very often impaired by missed doses, early termination or even non-initiation. These outcomes are also perceived to be clearly worse in real life than in a clinical trial setting.

Reformulation as Long Acting Injectables is seen as a powerful approach to improve the efficacy of multiple active pharmaceutical ingredients. These LAIs have the potential to create significant value for payers as well as for other key stakeholders in the health system. This value is found across a wide variety of indications from large chronic conditions such as diabetes or COPD to smaller highly specialized indications such as transplantation. It can result from primary or secondary prevention of acute events, from a better control of chronic progressive diseases or infections, or from a variety of other benefits created by increased adherence and efficacy, improved tolerability or a combination of those.

Payers demand clear evidence of patient-relevant benefit but are also realistic with respect to the data required and are willing to accept surrogate endpoints when justified. Moreover, they recognize that the benefits of LAIs are likely to be reduced in a trial setting and are willing to accept pragmatic trial designs and real-life cohorts to demonstrate value beyond that shown in randomized trials. With the appropriate evidence, payers express a high willingness to reward the increased value of LAIs through favorable coverage decisions and pricing. They widely consider that prices in the range of the branded active principles are realistic and that premium can be achieved in many cases.

GLOSSARY

ACEis	Angiotensin-Converting Enzyme Inhibitors
AEDs	Anti Epileptic Drugs
AMNOG	Arzneimittelmarkt- Neuordnungsgesetz (Benefit Assessemnt) (Germany)
ARBs	Angiotensin II Receptor Blockers
CCGs	Clinical Commissioning Groups (UK)
CKD	Chronic Kidney Disease
CMS	Center for Medicare & Medicaid Services (U.S.)
CNS	Central Nervous System
COPD	Chronic Obstructive pulmonary Disease
CV	Cardiovascular
DM	Disease Management
DOT	Directly Observed Therapy
DRG	Diagnosis-Related Group
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
GI	Gastro Intestinal
HbA1c	Glycated Haemoglobin
HRRP	Hospital Readmissions Reduction Program (U.S.)
ICS	Inhaled Corticosteroid
IOP	Intra Ocular Pressure
IPPS	Inpatient Prospective Payment System (U.S.)
LABA	Long Acting β2-Agonist
LAI	Long Acting Injectable
LAMA	long-acting muscarinic antagonist
LDL	Low Density Lipoprotein
LUTS	Lower Urinary Tract Symptoms
MA	Medicare Advantage (U.S.)
MTM	Medication Therapy Management
MTX	Methotrexate
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence
NNT	Number Needed to Treat
OAB	Overactive Bladder
OCAS	Oral Controlled Absorption System
OS	Overall Survival
PFS	Progression Free Survival
PK	Pharmaco Kinetic
QoL	Quality of Life
SubQ	Sub Cutaneous
T2DM	Type 2 Diabetes Melitus
TB	Tuberculosis
TNFs	Tumor Necrosis Factors
UTIs	Urinary Tract Infections
VGEFs	Vascular Endothelial Growth Factors
WHO	World Health Organization

METHODOLOGY

To gather payers' views on LAIs, a total of 26 interviews were completed with payers from the U.S., EU5, Latin America and Asia. Interviewees were real payers with budget allocation, reimbursement and pricing, formulary decisions and health technology assessment responsibilities.

Each interview lasted on average 60-75 minutes and loosely followed a discussion guide but the emphasis was on brainstorming potential value and understanding of the belief systems underlying interviewee's responses.

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