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White Paper

ASSESSING PERSON-CENTERED THERAPEUTIC INNOVATIONS

Are usage experience and outcome benefits from Person-Centered Therapeutic Innovations appropriately valued?

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ABOUT THIS WHITE PAPER

The White paper titled "Assessing Person-Centered Therapeutic Innovations" was developed by IQVIA Consulting Services, based on research conducted between June 2018 and September 2018.

The underlying research examines value of six types of therapeutic innovations by researching stakeholder perceptions of the various benefits offered by them. A value framework was proposed to support the research, calling out benefits of a therapeutic solution in terms of outcomes as established in current HTA processes, as well as usage experience in and of itself. Value of these benefits for stakeholders across the healthcare system, including payers, patients and their caregivers, physicians and healthcare providers, are studied through a combination of secondary and primary research.

The authors note that broad spectrum of benefits provided by these innovations are shared by innovations beyond the studied six innovation types. For purpose of this White paper, the term "Person-Centered Therapeutic Innovations" is adopted to refer to the researched therapeutic solutions as a group, reflecting composition of the added-value by them. The White paper also explores potential steps towards better reflection of the full value spectrum of the Person-Centered Therapeutic Innovations. Meanwhile, the authors also acknowledge that the insights and solutions recommended may have applicability beyond the six studied innovation types, and further exploration is required to determine this more precisely.

DISCLAIMER: The research is sponsored by the European Federation of Pharmaceutical Industries and Associations (EFPIA)

EXECUTIVE SUMMARY

Follow-on drugs, drug plus drug combinations, drug reformulations, drug repositioning, drug plus digital applications and drug plus device combinations account for a significant proportion of medical innovations and have long been recognised as an integral part of the innovation pathway. They provide benefits for stakeholders across the healthcare system, such as patients and their caregivers, physicians and payers. They can also benefit the healthcare system through greater price competition resulting in cost savings.

These innovations are referred to as Person-Centered Therapeutic Innovations in this White paper, reflecting composite of the improvements that they tend to provide to the value for stakeholders from both usage experience and outcome perspectives. On the one hand, outcome consists of clinical, cost and efficiency measures, many of which have institutionalised assessment methods. On the other hand, usage experience deals with the journey to reach the outcomes. Usage experience related benefits have value in and of themselves and sometimes can translate directly or indirectly into outcome benefits. For instance, reduction in patient burden can lead to better compliance, resulting in better efficacy, and can also improve patient sense of wellbeing and happiness. Person-Centered Therapeutic Innovations deliver benefits across these outcome and usage experience aspects, with the more substantial increments generally occurring in the latter dimension. While outcome benefits tend to be easily identifiable and valued, assessing usage experience requires a deeper understanding of how patients experience their condition and treatment.

This report examines how the benefits offered by the Person-Centered Therapeutic Innovations are perceived using an approach comprising of extensive secondary and primary research.

While not the primary focus of this White paper, it is important to note that First-in-Class products are also covered by the value framework proposed.

First-in class products often also provide benefits across both dimensions, although proportionally speaking, outcome benefits tend to be more front and centre in defining their value profiles, at least in the current value assessment environment. While this White paper uses Person-Centered Therapeutic Innovations to refer to the six types of innovations, we acknowledge that the full spectrum of benefits and values to stakeholders mentioned in this paper are indeed applicable to all types of innovations, and it is the authors' conviction that there is scope to explore holistically, across all types of innovations, how value should be defined and appreciated. This White paper takes an exploratory step in this direction.

PERCEPTION OF PERSON-CENTERED THERAPEUTIC INNOVATIONS

Research conducted suggests there is a discrepancy in the perception of value offered by Person-Centered Therapeutic Innovations between payers and final users (i.e. patients/physicians). Frequently, payers perceive Person-Centered Therapeutic Innovations as not adding value over existing therapies, while patients and physicians find both the usage experience and outcome benefits of these innovations to be important additions. This difference in perceptions is particularly stark for innovations such as drug reformulations and drug plus device which are seen very positively by patients as they tangibly improve their daily lives, while payers dismiss them as lifecycle management by manufacturers.

EVALUATION OF PERSON-CENTERED THERAPEUTIC INNOVATIONS

A new therapeutic solution generally follows a three-step process prior to reaching patients and physicians: Health Technology Assessments (HTAs); pricing and reimbursement negotiations and finally, patient access. Although, in some countries and for certain types of therapies, there may not be a clear separation between the HTAs and pricing and reimbursement process with both taking place simultaneously or the focus being mainly on the price.

A higher proportion of products covered under the Person-Centered Therapeutic Innovation concept in this White paper receive negative HTA decisions compared to first-in-class products. Pricing and reimbursement results for these Person-Centered Therapeutic Innovations tend to be less favourable than first-in-class products. The HTA decisions and pricing and reimbursement can impact patient access as well. The evaluation of these Person-Centered Therapeutic Innovations in these three steps contrasts with the evaluation by patients and physicians who incorporate the benefits of Person-Centered Therapeutic Innovations into their drug choice decision making.

HTA decisions: Current HTA mechanisms can undervalue the benefits of these Person-Centered Therapeutic Innovations, both in terms of outcomes and usage experience benefits. Firstly, HTA bodies' current methodologies do not consider usage benefits in their own right, but only through the lens of outcome benefits. Even in these cases, usage benefits are often criticised as being surrogate endpoints or not patient relevant. It should be acknowledged that there is some variation in the level of discussion around usage benefits across countries. In some cases, patient reported experiences may be brought up through patient representatives in HTA discussions (for example, in NICE discussions in the UK) but they are generally not a driving factor of the final outcome. Secondly, evidence related to outcome benefits from Person-Centered Therapeutic Innovations is not often available at launch because it requires longer term collection throughout the product's lifecycle. While some countries do have a process to re-examine therapies, there is generally no clear mechanism to revaluate the price and access of a therapy based on post launch data, even if it shows value on the measures considered important by payers. Person-Centered Therapeutic Innovations can also bring broader indirect societal outcome benefits (such as reduction in absence from work) which are not considered in most countries. Finally, in some countries (such as Italy), many types of Person-Centered Therapeutic Innovations may not be subject to HTAs at all and thus, their full set of benefits are not evaluated leading to access decisions being made purely on prices.

Pricing and reimbursement: Additionally, there is a general expectation from payers that these products should be priced lower than first-in-class products unless they show substantial improvements in clinical or cost outcomes. Overall, the usage experience benefits are not considered during price discussions. The price and reimbursement of these products often does not take into account their outcome benefits (such as better adherence) due to the lack of acceptance of post launch data for renegotiation of price.

Patient access: The HTA and pricing and reimbursement discussions can impact the access to Person-Centered Therapeutic Innovations due to lack of inclusion of full set of benefits in valuation of Person-Centered Therapeutic Innovations. Firstly, it can lead to a lack of reimbursement which results in fewer patients having access to therapies which could offer relevant value. Secondly, a less positive HTA decision (such as ASMR V in France or no innovation rating in Italy) can result in lack of funding

at the hospital level. This may result in hospitals being unable or unwilling to place a therapy on formulary which, in turn, impacts patient access. Finally, a lack of inclusion of full set of benefits in the valuation of Person-Centered Therapeutic Innovations can lead to a low reimbursed price resulting in limited manufacturer launch.

While the above discussion suggests that HTA and pricing mechanisms may not fully capture the spectrum of values offered by Person-Centered Therapeutic Innovations, an absence of validated evidence collection mechanism demonstrating the usage experience values also prevents HTA bodies and payers from appropriately assessing them. This creates a conundrum for manufacturers as they are apprehensive about investing in collection of usage value evidence without a mechanism to incorporate them in HTA and price decision making.

The difference in the value perception and evaluation between payers and final users suggests that there is a need to reassess the HTA and pricing and reimbursement mechanism for Person-Centered Therapeutic Innovations. While the position of HTA bodies and payers is currently focused on outcomes assessment, regulatory bodies are paving the way for a broader assessment of therapies and their full set of benefits, including the usage experience. An HTA and pricing and reimbursement body of the future will need to revisit their position on usage experience to be ready to evaluate such products. With that in mind, the following recommendations can help the healthcare stakeholders move towards a more holistic assessment of benefits offered by Person-Centered Therapeutic Innovations –

- **Enhance involvement of final users (e.g. patients and physicians) in HTA and pricing and reimbursement decision making:** Earlier involvement of users (particularly, patients) in the disease scoping process and provision of voting rights in access and reimbursement decision making
- **Holistically evaluate value over a product's lifecycle and be receptive to additional data to reassess a product's value post-launch:** Acceptance of post-launch data and re-evaluation of HTA decisions and pricing and reimbursement decisions based on new evidence
- **Better understand the value of usage experience benefits:** Clear identification of direct and indirect benefits from user (especially, patient) experience value and development of validated measurement tools which can measure these benefits
- **Explore feasibility of appropriately rewarding the studied Person-Centered Therapeutic Innovations with a multi-stakeholder approach:** Dialogue between all stakeholders in the healthcare system to discuss the relevance and requirements for rewarding the values associated with a more holistic set of benefits

Regulators have called for more patient and user centric development of therapeutic solutions and have specifically mentioned innovations falling into Person-Centered Therapeutic Innovations as important from a public health perspective. There is a need for other decision-making stakeholders such as payers and policy-makers to consider the value of these solutions and focus on collecting evidence to demonstrate this value and on rewarding solutions that have the appropriate evidence. Based on current methodologies, adjusting to the future state will require authorities to broaden their spectrum of benefits considered and identify appropriate ways to value the benefits that are most important to patients.

INTRODUCTION

Innovations by the pharmaceutical industry are widely credited for improving health and wellbeing of patients, enhancing healthcare management for physicians and increasing budget savings for payers ((Deloitte, 2016) (Prata, 2015) (Petrova, 2014)). These innovations can take place in multiple forms such as first-in-class, follow-on, drug plus drug combinations, drug reformulation, drug plus device or drug plus digital applications (Table 1) (Lybecker, 2014) (Lundbeck, 2013) (Molinari, 2012)) (Murteira, Millier, & Toumi, 2014).

Table 1: Types of Innovations in the Pharmaceutical Industry with Definitions

FIRST-IN-CLASS	New chemical or biological entities launching in a class where no drugs previously existed
FOLLOW-ON	New chemical or biological entity that contains an active pharmaceutical ingredient that is structurally similar to an existing chemical or biological entity and is targeting the same indication with a comparable mechanism of action. Additionally, for the purposes of this research, if a product received EMA approval within 18 months of the first-in-class product then it will not be a part of this category.
DRUG REPOSITIONING	A new indication for a chemical or biological entity that was already on the market for another indication and had matured in that indication – the product gained the new indication in a new therapy area (new ATC code)
DRUG REFORMULATION	Reformulation of a drug that was already on the market (e.g. IV to SC, oral to inhaled, immediate release to extended release)
DRUG PLUS DRUG	Combinations of drugs already on the market (e.g. single pill combinations)
DRUG PLUS DEVICE	Combination of a drug that is already on the market with a device to improve administration
DRUG PLUS DIGITAL APPLICATION OR DIGITAL THERAPIES	Combination of a drug that is already on the market with a digital device/app to improve administration, compliance, monitoring, etc. Stand-alone apps that can be used across drugs are also considered

Each of these types of innovation can bring added value over existing treatment options across stakeholders in the health system, namely, payers, patients and their caregivers, and physicians. Assessing the innovations listed in Table 1, the value propositions of first-in-class innovations generally have their main focus on the clinical efficacy and these innovations usually represent a large step forward on this dimension compared to the previous standard of care (Lanthier, Miller, Nardinelli, & Woodcock, 2013).

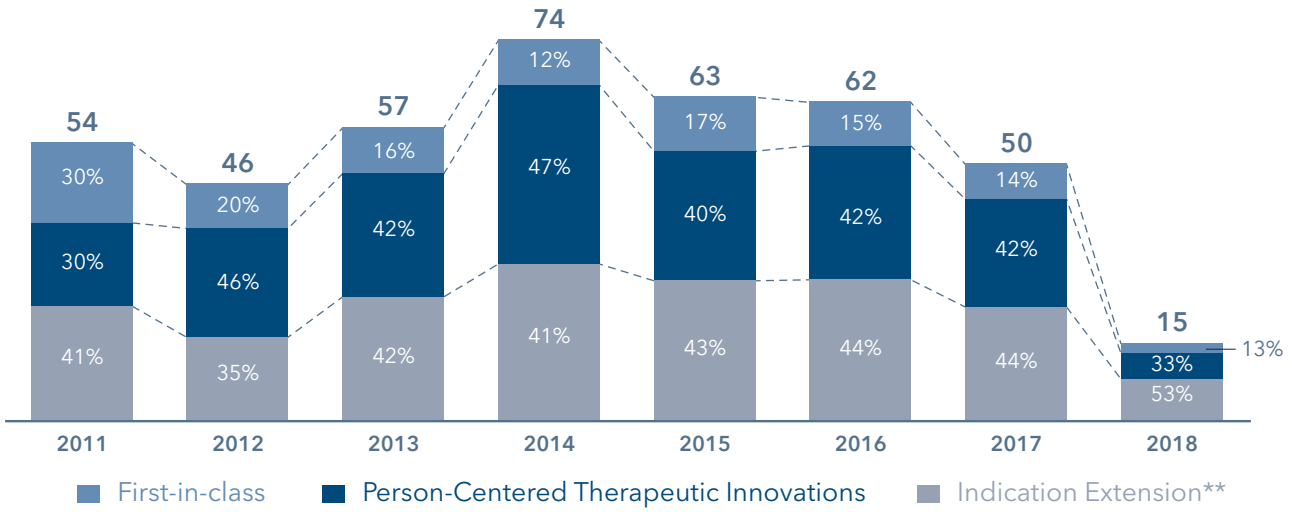
The other types of innovation in Table 1 offer enhancements over existing therapies across several dimensions. A few examples of added benefits from these innovations are given below (not exhaustive) (Lohse, 2018) (Toumi & Rémuzat, 2017) (Lybecker, 2014) (GSK, 2014) (Lundbeck, 2013) (IFPMA, 2013) (Network, 2005)

- **Drug reformulation** from intravenous to sub-cutaneous can avoid long drives to hospitals and lengthy stays for patients as well as, save costs for the healthcare system by reducing hospital stays. It can also enhance compliance and efficacy for patients.
- **Follow-on drugs** can have an improved AE profile, and thereby improving patient experience and allowing for a broader set of patients to benefit from that class of drugs.
- **Drug + drug combinations** can reduce the dose burden for patients of chronic illnesses and help with efficient management of the disease for both physicians and patients. This can also result in better compliance and thereby improved efficacy.
- **Drug + device and drug + digital** can improve patient-physician interaction which in turn can lead to more efficient healthcare management, and enhanced patient confidence in physician interactions.
- **Drug repositioning** can reduce overall healthcare costs and represents efficient use of existing resources as drugs which are already available on the market are used for new purposes.

In this White paper, we refer to these six types of innovations as Person-Centered Therapeutic Innovations. **While taking different forms, the Person-Centered Therapeutic Innovations are a selected (see Table 1) range of therapeutic innovations that enhance value for the healthcare system by improving usage experience of persons involved (i.e. patients, their caregivers and healthcare service providers), and often also directly or indirectly delivering outcomes benefits.**

First-in-class products can also improve usage experience and deliver outcome benefits for persons involved. In this White paper, we focus on the six types of innovations listed under Person-Centered Therapeutic Innovations to understand the full spectrum of possible benefits from a therapy better, with acknowledgement that the underpinning full spectrum of benefits would apply across all types of innovations.

Figure 1: Percentage of First-in-class, Person-Centered Therapeutic Innovations and Indication Extension Products: 2011-2018



Notes: **Indication extensions were defined as a separate category as these were drugs which were already on the market and expanded into indications within the same therapy area (ATC code); Based on EMA approval; Disease areas: Antiviral, CNS, Diabetes, Multiple Sclerosis, Oncology, and Respiratory.

Source: IQVIA proprietary data and research

Person-Centered Therapeutic Innovations are common in the industry with, around 40% of all therapies launched between 2011 and 2018 falling into this category (See Figure 1). If we exclude indication extensions, Person-Centered Therapeutic Innovations constitute 65-70% of the total new therapies launched in a year. Break-through therapies are rarer and Person-Centered Therapeutic Innovations potentially offer continous improvements for healthcare stakeholders. The cumulative impact of these advancements enhances meeting of stakeholder needs and leads to radical improvements in healthcare management (Langer, 2016) (Lybecker, 2014) (Lundbeck, 2013). This step-wise pathway of continuous innovation leading to periodic radical breakthroughs has been well acknowledged previously across other industries as well (Rosenberg, 1986) (UNIDO, 2016) (Rayna & Striukova, 2009). Making regular, continuous improvements is a concept that has been used effectively in multiple sectors. The term 'Kaizen' is used regularly in these sectors to describe these types of enhancements and is a standard approach to innovation in many industries. This continuous chain of improvements can lead to radical changes, 'Kaikaku'.

Acknowledging the high level of activity relating to Person-Centered Therapeutic Innovations and potential benefits offered by them, the research informing this White paper explores the value of these therapies in more detail. In particular, the key motivations for this research are to answer the following:

- **How are various benefits of these products expressed, and how do they impact different stakeholders in the healthcare ecosystem?**
- **Do discrepancies exist in stakeholder perceptions of the benefits of these products? If yes, how and to what extent do these discrepancies affect effectiveness and/or efficiency of healthcare systems?**
- **Is there a case for adapting/improving relevant decision-making processes and criteria based on findings from the above set of questions?**

METHODOLOGY

VALUE FRAMEWORK FOR ASSESSING PERSON-CENTERED THERAPEUTIC INNOVATIONS

The different types of value associated with Person-Centered Therapeutic Innovations needed to be identified and characterized to answer the research questions. Value was identified based on prior academic research and an assessment of Person-Centered Therapeutic Innovations that launched between 2011 and 2018 (Figure 2). The benefits of Person-Centered Therapeutic Innovations were then organized into a value framework that was specifically developed to facilitate primary research discussions. In summary, the key areas of value identified for each stakeholder group include (not exhaustive):

- **Patients, family and caregivers:** These innovations provide value to patients by improving their overall experience. This value has spill-over effects for patients as it improves their day-to-day interactions, overall convenience and can lead to tangible benefits for their daily lives. This can, at times, improve treatment adherence, potentially leading to meaningful direct and indirect outcome benefits for the patient, patient's family/caregiver and overall healthcare system ((Wertheimer, 2001), (Toumi & Rémuzat, 2017)).
- **Physicians:** The entry of follow-on drugs helps expand the understanding of the class and provides physicians with more products that they can target to patient sub-sets (Wertheimer 2001, Lee 2004, Jena et al 2009). For example, various Beta Blockers entered the same class but responded differently based on other medications that patients were taking, thus different drugs were more suited for different cohorts of patients (Lybecker, 2014).
  - » Another interesting example finds that in classes with multiple follow-on drugs, the demand for first-in-class does not increase even after its patent expiry and subsequent price decrease (Jena,2009). These findings are unaffected

by insurance, marketing, switching costs. This suggests that the follow-on products provide value to the users that cannot be discounted.

- **Payers:** From a healthcare system perspective, the entry of new solutions in the same class promotes price competition which results in cost savings in the long run. They can also lead to additional outcome benefits at a lower cost (Lee, 2004).

Figure 2: Summary of Benefits by Stakeholder Based on Literature Review

Patient/Caregiver perspective	Health system perspective	Industry perspective
Higher efficacy (First-in-class may not be best-in-class efficacy)	Overall budget saving due to the patient benefits	Balanced portfolio
More suited treatments for specific patients	Price competition	
Improved safety/tolerability (fewer AEs)	Better understanding of the class	
Enhanced adherence	Simplified monitoring by physician	
Improved patient convenience/QoL		
Lower burden on caregiver		

The assessment of products launched between 2011 and 2018 coupled with the values identified from the literature resulted in a comprehensive value framework (See Figure 3). This value framework has three levels –

- **Value dimensions:** At the topmost level, value of a therapeutic innovation is considered two-dimensional, outcome versus experience. While outcome concerns the end result, experience deals with the journey to reach the outcome. These aspects cumulatively define the overall set of values for the users of these therapies, namely the patients, caregivers and physicians. Both dimensions are relevant across all healthcare system stakeholders.
- **Value expressions:** The value of a therapeutic innovation can be categorised into six benefits and experiences, which form the second level of the framework. Under the outcome dimension, clinical outcome benefit represents the end results of a treatment that are captured directly, the cost benefit represents the financial savings that result from these therapies and efficiency benefits deal with outcomes that result from efficient use of available resources. Under the experience dimension, the benefits are grouped by the type of user i.e. patients, physicians and providers.
- **Value drivers:** Finally, the third level shows the specific benefits that a therapy can provide that leads to the expression of a value. For example, under the outcome dimension, improvements in efficacy lead to a clinical outcome benefit. Similarly, on the experience side, all drivers enhance the experience of patients, physicians or providers. The experience dimension has value on its own and can also lead to outcome benefits such as improved compliance and efficacy.

Figure 3: Value Framework

VALUE DIMENSION	Outcome			Experience		
VALUE EXPRESSION	Clinical outcome benefit	Cost benefit	Efficiency benefit	Patient/family Experience	Physician Experience	Provider Experience
VALUE DRIVERS	Efficacy benefit	Cost effectiveness	Reduced R&D costs	Lower dose burden	Reduced additional testing	Reduced resource/facility use
	AE/safety benefit	Reduced budget impact	Efficient resource use	Reduced travel/ time off work	Easier storage	
	HRQoL benefit	Price reduction due to competition	Enhanced value of existing drug(s)	More informed and efficient physician interaction	Better visibility on patient self-care	
				Easier administration/ use	More treatment options	
				Improved patient psychology and confidence in drug use		

This value framework forms the conceptual base for this White paper. The values shown on the framework have been used to assess Person-Centered Therapeutic Innovations and understand the appreciation of values provided by these innovations.

This value framework aims to capture the experience benefits for all key stakeholders in the healthcare ecosystem, namely, patients, caregivers, physicians and providers. Other value frameworks like Fastercures PPVF and ICER have acknowledged the importance of experience related benefits as well. Fastercures PPVF focuses on patient experience through the categories of patient preference and patient reported outcomes. Patient reported outcomes category captures the patient experience by assessing the complexity of regimen which includes patient burden (eg. dosing, travel time), treatment interface (eg. logistics, caregiver interactions) and quality of life which includes cognitive and psychological status. The patient preference category allows patients to apply weights to above mentioned based on their individual preference and importance. ICER acknowledged the value of experience benefits under 'other benefits and contextual considerations' but has not directly included them as the impact on cost effectiveness is hard to quantify (See appendix for details).

RESEARCH APPROACH OVERVIEW

Informed by the Value Framework, the supporting research for this White paper was undertaken in two steps, as summarised in Figure 4.

Step 1: targeted literature review and HTA report assessment

In the first step, a targeted literature review was conducted regarding positions expressed by different stakeholders towards the innovations that fall under Person-Centered Therapeutic Innovations. Payers, physicians, patients, manufacturers and academics were the stakeholders of interest. Manufacturers and

academics had published opinions on innovations that fall under Person-Centered Therapeutic Innovations while physicians have not directly expressed opinions on these innovations. However, some academic research captured the physician's opinions on the values offered by Person-Centered Therapeutic Innovations.

Payers have, also, not published a specific opinion on this topic but HTA reports are key sources to understand the payer point of view. A total of 960 HTA reports (From 2011 to 2018) were reviewed from 8 European countries and across 6 disease areas, focusing on the following (Details in Appendix) –

- HTA and pricing and reimbursement results for Person-Centered Therapeutic Innovations vs first-in-class products
- Value elements (corresponding to "value drivers" in the Value Framework – Figure 3) considered in the HTA process used in these markets.

Figure 4: Summary of Research Process

Ex-payers were interviewed to understand payer perspectives; Patient representatives were interviewed to understand patient perspectives

These 8 countries were selected based on market size and because they represent a breadth of healthcare systems and geographic spread across Europe. The 6 disease areas were selected based on the market size and the types of innovation taking place within them.

Gaps in the published opinions of patients, physicians and payers were filled through primary research.

Step 2: multi-stakeholder interviews

In the second step, primary research was conducted with multiple stakeholders in the healthcare system (See Figure 4 for details) to address information gaps in secondary research. The value framework was used to guide the primary research with each stakeholder in the following manner –

- Each stakeholder assessed the importance of each value driver and expression.
- Each stakeholder was also asked to rate the level of importance of the additional values from the case study products.
- Finally, the rationale behind the value recognition in the payer assessments was discussed.

Case studies

Deep dive case studies were compiled for 6 Person-Centered Therapeutic Innovations, with inputs from both steps mentioned above –

- Step 1: Each product's key value proposition was examined and highlighted on the value framework
  - » Following this, the key value recognised by payer assessment reports was noted.
  - » Publicly available payer assessments were evaluated across countries and disease areas in scope.

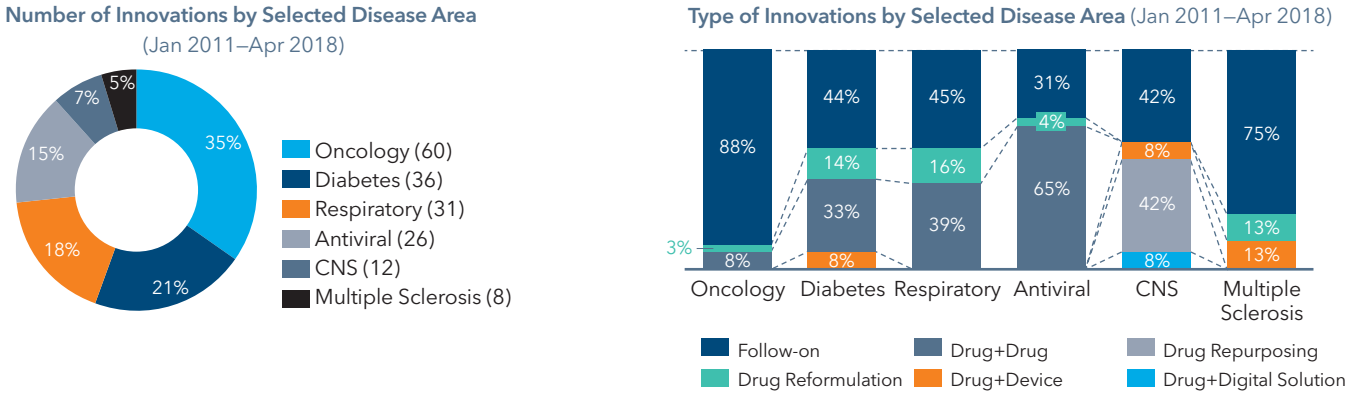
- Step 2: The value of these products was assessed with patients, physicians and payers in the primary research

There were data limitations with availability of regional level payer assessments and the level of detail in the payer assessments varied across countries[1].

PERSON-CENTERED THERAPEUTIC INNOVATIONS – PERCEPTION AND EVALUATION

As discussed earlier, Person-Centered Therapeutic Innovations are common in the industry and form a key part of the innovation cycle, offering continuous improvements. Person-Centered Therapeutic Innovations are comprised of multiple types of innovation (Table 1) and if one looks across these types, follow-on products are the most common overall, accounting for 55% of new products in Person-Centered Therapeutic Innovations between 2011 and 2018 (average across disease areas). The type of Person-Centered Therapeutic Innovations varies by disease area (See Figure 5). For example, in chronic diseases such as Diabetes, Respiratory or HIV, we see a larger percentage of Drug + Drug combinations, potentially driven by the high dose burden for patients which impact the patient's experience and play a role in adherence. In Oncology, since different patients often respond to different drugs within the same class, there is a higher percentage of follow-on products.

Figure 5: Number and Type of Person-Centered Therapeutic Innovations by Disease Area



Notes: Based on EMA approvals; Disease Areas: Antiviral, CNS, Diabetes, Multiple Sclerosis, Oncology, Respiratory
Source: IQVIA HTA Accelerator, EMA

Given that these innovations are frequent and appear to target specific needs by disease area, there is a need to assess the benefits provided by them in a real world setting in more detail. This section discusses our findings on perception of value of Person-Centered Therapeutic Innovations, overall and on relevant specific values across stakeholders. Following this, the paper documents stakeholders' actual evaluation of Person-Centered Therapeutic Innovations prior to reaching the final users, in terms of HTA results, pricing and reimbursement and patient access decisions.

1 For example, UK, France and Germany provide detailed assessments while the assessments in Spain are much more limited

STAKEHOLDER PERCEPTION OF PERSON-CENTERED THERAPEUTIC INNOVATIONS

The benefits shown on the Value Framework are acknowledged by all stakeholders, but the level of value attributed to these benefits differs between payers and other stakeholders

To form a common foundation when discussing value, the Value Framework as illustrated in Figure 3 was explored in interviews with stakeholders.

All stakeholders agree that types of benefits captured in the Value Framework are relevant and represent the full spectrum of benefits that can be associated with a therapeutic innovation.

Both outcome and usage experience dimensions were considered relevant by all stakeholders and they agreed that the benefits listed under them are regularly associated with therapies. Stakeholders also acknowledged that usage experience was relevant in and of itself and may also lead to benefits on the outcome dimension.

However, payers differ from patients and physicians in what benefits are of value (Figure 6, Figure 7).

For payers, the outcome dimension is more important, while the experience dimension does not feature strongly in their perception of value. Payers, nevertheless, acknowledge that these benefits can be important for a patient as they relate to improving the patient's daily life. On the other hand, patients and physicians agree that while clinical outcomes are important, the experience dimension is a key determinant of how they perceive a therapy. These benefits are necessary determinants of the patient's broader wellbeing. The types of daily activities one therapy allows a patient to do versus another; the burden one therapy might cause versus another; the way in which a user interacts with the therapy are all important elements that are taken into consideration by both patients and physicians; as they improve the patient's overall experience and can lead to better adherence and long term better outcomes.

Figure 6: Ranking of Key Value Drivers by Stakeholders in Primary Research

Rank	Payer	Clinical KOL	Patient Rep
1	Efficacy benefit	Efficacy benefit	Efficacy benefit
2	Cost effectiveness	AE/safety benefit	AE/safety benefit
3	Reduced budget impact	Low dose burden	Improved patient psychology and confidence in drug use
4	AE/safety benefit	More treatment options	More informed and efficient physician interaction
5	Price reduction due to competition	HRQoL benefit	Low dose burden

For patients the experience value from reduced dose burden, improved interaction with physicians and overall psychological benefits is very important

Key value drivers not considered important by payers

Notes: KOL – Key Opinion Leader; Source: Stakeholder interviews (n=27); Disease areas: Antiviral, CNS, Diabetes, Multiple Sclerosis, Oncology, Respiratory; Countries: UK, Germany, France, Spain, Italy, Netherlands, Sweden, Poland

Figure 7: Rating of Importance of Value Expressions by Stakeholder

	PAYER	PATIENT REP	CLINICAL KOL
Clinical outcome benefit	HIGH	HIGH	HIGH
Cost benefit	HIGH	LOW	LOW
Efficiency benefit*	LOW	LOW	MODERATE
Patient/family experience	LOW	HIGH	HIGH
Physician experience	LOW	MODERATE	HIGH
Provider experience	LOW	LOW	HIGH

For payers, experience benefits are not important, and focus remains on clinical outcomes and costs
Patients and clinicians on the other hand place high importance on experience related factors

Notes: KOL – Key Opinion Leader; Source: Stakeholder interviews (n=27); Disease areas: Antiviral, CNS, Diabetes, Multiple Sclerosis, Oncology, Respiratory; Countries: UK, Germany, France, Spain, Italy, Netherlands, Sweden, Poland
* Efficiency benefit refers to the benefit from the therapy which leads to the efficient use of available resources in the overall healthcare system

Exhibit 1: Quotes from Stakeholders on Perception of Person-Centered Therapeutic Solutions

"I can see why the experience dimension would be important for patients but I am mostly focused on the clinical outcomes and the cost savings." **- Payer**

"While we appreciate an improvement in safety profile…these are generally not too important if not accompanied with improvements in efficacy." **- Payer**

"I have spoken to cancer patients that find parking stressful and a treatment that saves them a trip reduces stress. Patient psychology is very important, if a treatment is improving the overall patient happiness over and above the efficacy then that will be valued very highly."
- Patient Representative

"Some new devices and digital additions give us much more confidence that a patient is taking the drug correctly." **- Clinical KOL**

Source: Stakeholder interviews (n=27); KOL – Key Opinion Leader

The perceived level of additional value attributed to the types of Person-Centered Therapeutic Innovations varies greatly across different stakeholders

Using the perceptions of the benefits from the Value Framework as a base, stakeholders (payers, patients and physicians) expressed their perception of each of the types of Person-Centered Therapeutic Innovations.

Unlike first-in-class products which are perceived strongly by all stakeholders, **payers consistently indicate a lower perception of value across all types of Person-Centered Therapeutic Innovations compared to patients and physicians.** Payers dismiss a number of these innovations as lifecycle management activities by the industry. However, patients and physicians note that these innovations are addressing shortcomings in the existing therapies and can expand the use of therapies and healthcare management. Physicians also note that the first-in-class may not always be the best therapy for all patients both on efficacy and ease-of-use dimensions. (See Figure 8). Physicians prefer therapies that are more convenient as they are more confident that patients will use them regularly, resulting in more efficient overall healthcare management.

Figure 8: Perception of value of each type of Person-Centered Therapeutic Innovations across stakeholders

Type of Product	Perception of the level of additional value			Benefits from product type (for an average product)
	Payer	Patient	Clinical KOL	
First-in-class products	HIGH	HIGH	HIGH	• All stakeholders view these products as providing clinical benefits and are perceived to have relevant meaningful value
Follow-on product in an existing class	MEDIUM	HIGH	HIGH	• Payers believe these products offer marginal improvements • Physicians value these products substantially more as they provide additional options for treating patients • Patients value improvements in usage experience
Drug Reformulation	LOW	HIGH	HIGH	• These types of innovation are seen as nothing more than a lifecycle management tool by payers • Physicians and patients value it greatly as it reduces resource burden and improves patient convenience
Drug+Drug	LOW	MEDIUM	MEDIUM	• Payers perceive Single Pill Combinations only as an improvement in convenience which is not rewarded • Patients and physicians value this convenience highly when dose burden is high and in particular in CNS diseases
Drug Repositioning	HIGH	HIGH	HIGH	• Payers believe drug repositioning could lead to results similar to first-in-class as the value depends on the clinical benefit in a new indication
Drug+Device	LOW-MEDIUM	HIGH	HIGH	• Payers do not value ease of administration or enhanced physician-patient interaction unless efficacy benefits are demonstrated • Devices help physicians with monitoring and can ease administration burden for patients
Drug+Digital	MEDIUM	HIGH	HIGH	• Payers have limited experience with reimbursing digital devices, however, if they show efficacy benefits, they may achieve a price premium

Notes: KOL – Key Opinion Leader; Source: Stakeholder interviews (n=27); Disease areas: Antiviral, CNS, Diabetes, Multiple Sclerosis, Oncology, Respiratory; Countries: UK, Germany, France, Spain, Italy, Netherlands, Sweden, Poland

A disconnect between patients and physicians on the one hand and payers on the other hand was highlighted in the case of Genvoya™ and Relvar Ellipta™, where benefit in the form of reduced user burden due to reduced renal testing and ease-of-use respectively were viewed as important by patients and physicians, while payers did not perceive these to bring additional value over existing treatments.

STAKEHOLDER EVALUATION OF PERSON-CENTERED THERAPEUTIC INNOVATIONS

Following the perception discussion, the research also explored how Person-Centered Therapeutic Innovations are evaluated by the health systems, a concept that captures the following:

- What level of value was seen in the HTA process,
- How this value translates into pricing and reimbursement status of these products, and
- Finally, how successful these products are in achieving patient access.

This research is based on the HTA reports, overall price and sales based on IQVIA MIDAS data and interviews with the stakeholders.

In some countries, such as France and Germany, there is a clear separation between HTAs and pricing and reimbursement decisions with separate bodies involved in each of these decisions. In other cases, there may not be a clear separation between the initial assessment body and the final price decision maker/ budget holder as both these discussions take place simultaneously. Finally, there are countries, such as Spain, where the HTAs are done at a national level but they serve only as recommendations and the final price and access decisions are made at the regional level. This paper first analyses the HTA decisions for Person-Centered Therapeutic Innovations and then assesses the price and reimbursement decision making by the final budget holder separately.

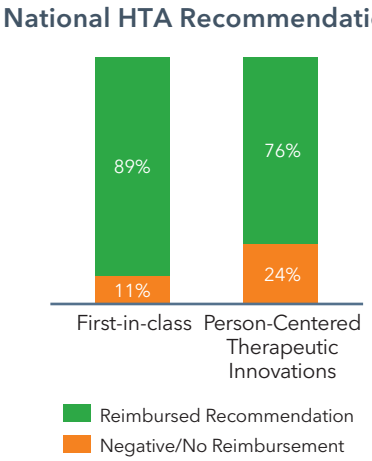
HTA decisions for Person-Centered Therapeutic Innovations are more negative on average versus first-in-class products

HTA decisions for Person-Centered Therapeutic Innovations and first-in-class products were assessed to understand the level of value associated with these products during their evaluation. Person-Centered Therapeutic Innovations and first-in-class were compared to assess whether the products were reimbursed or not. In some countries, the national HTA decisions may not directly impact access but they serve as recommendations for regional/local authorities. In our analysis, if the national HTA decision was not favourable then it was placed in the 'negative' category.

The HTA decisions were explored in more detail using the case studies to assess what types of value are included in the discussions. Our analysis showed that first-in-class products generally receive positive HTA decisions due to their efficacy advancements. However, Person-Centered Therapeutic Innovations receive a negative HTA decision[2] in about 25% of cases, on average across the 6 disease areas (Figure 9).

2 A negative HTA decision means the product received a negative assessment in the national payer report, this may result in no reimbursement in certain countries or act as a recommendation for further assessments at regional level. Germany was excluded from this analysis and has been mentioned separately in Figure 10. In France a negative decision is equivalent to SMR insufficient, however, an ASMR V may also represent a negative decision (See Patient access)

Figure 9: National HTA Recommendation Over Time – 6 Disease Areas In-Scope (Jan 2011 – Apr 2018); First-in-Class vs. Person-Centered Therapeutic Innovations

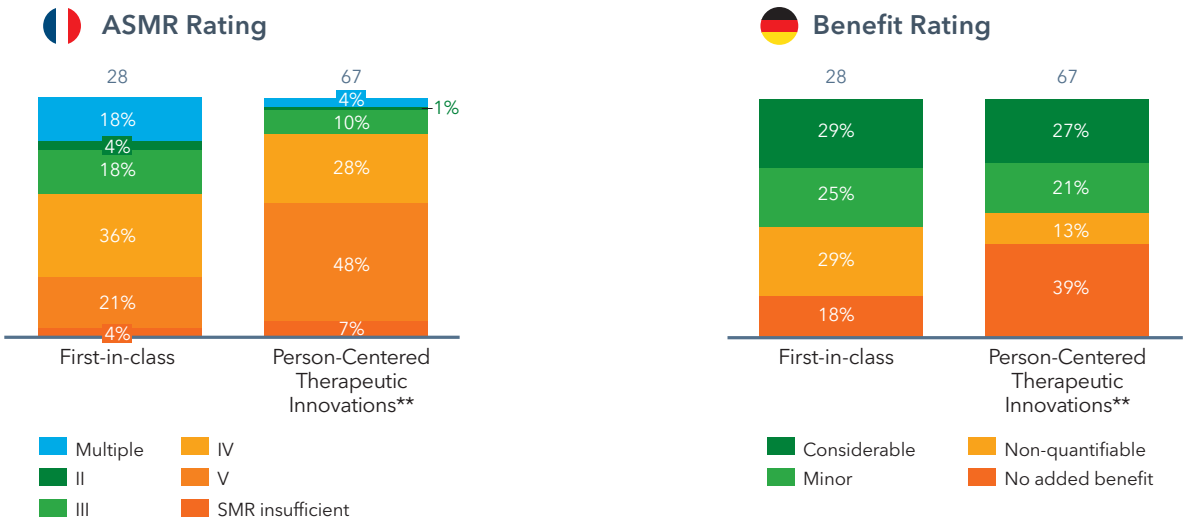


Note: Germany was excluded as the payers do not make a direct decision on reimbursement; Indication extensions were not considered for this analysis. A negative HTA decision means the product received a negative assessment in the national payer report, this may result in no reimbursement in certain countries or act as a recommendation for further assessments at regional level.

Notes: KOL – Key Opinion Leader; Source: IQVIA HTA Accelerator; Disease areas: Antiviral, CNS, Diabetes, Multiple Sclerosis, Oncology, Respiratory; Countries: UK, Germany, France, Spain, Italy, Netherlands, Sweden, Poland

In France and Germany, there are clinical ratings of added value for the Person-Centered Therapeutic Innovations. This allows us to assess how these products were evaluated in more detail. Overall, Person-Centered Therapeutic Innovations receive a much higher percentage of ASMR V ratings (no improvement) in France or no added benefit ratings in Germany. This implies that, based on the HTAs, these products do not offer additional value over existing treatments (Figure 10) and are, therefore, disadvantaged in subsequent pricing negotiations, as discussed in the next sub-section.

Figure 10: ASMR Rating in France and Benefit Rating in Germany for First-In-Class and Person-Centered Therapeutic Innovations



Note: Disease areas: Antiviral, CNS, Diabetes, Multiple Sclerosis, Oncology, Respiratory;
***Note: Multiple ASMR ratings cases are ones where a different ASMR rating was given to different sub-populations; For the ASMR and Benefit rating charts, we have restricted the sample here to the same set of products across both countries. Time Frame – Jan 2011 – Dec 2017*

Patients and physicians have evaluated Person-Centered Therapeutic Innovations more positively and do not always agree with the HTA decisions. They view the benefits from Person-Centered Therapeutic Innovations as differentiated from the first-in-class in meaningful ways. For example, Genvoya™ has been included in international HIV clinical guidelines and has seen real world usage suggesting that clinicians and patients have appreciated the value over other treatments due to its reduction in patient burden (See Appendix). This contrasts with the ASMR V and no added benefit rating it received in France and Germany respectively.

The clinical factors are the major drivers of HTA decision making and, in some cases, the only factors considered. Usage experience value is generally not considered by HTA

The drivers of their HTA methodology fall under either the clinical outcomes or cost benefit outcomes category. The other types of benefits were not considered important or taken into account. In particular, experience values were considered least important unless they could be translated into traditional clinical or cost benefits. **The lack of incorporation of the full set of values into HTAs and subsequent reimbursement or pricing decisions is largely consistent across the countries in scope. Usage experience related values are rarely mentioned in assessment reports as drivers of the final decision (See Figure 7).**

On the other hand, patients and physicians are looking for a change in the HTA process. Most physician key opinion leaders and patient association group members believe that usage experience value is meaningful and should be integrated into HTA (Figure 11). They note that Person-Centered Therapeutic Innovations can lead to tangible direct and indirect benefits for the healthcare system and society in the long run due to their enhancement of existing therapies. Physicians believe that not integrating the values associated with these innovations represents a 'missed opportunity' for payers to promote better patient wellbeing.

Another key reason for the lack of incorporation of these values stated is that evidence related to these values is rarely provided at the time of HTA. However, even if such evidence is provided, there is no clear mechanism to include it in the HTA decision making. This can create a challenge for the manufacturers because developing this evidence requires time and resources but there is no certainty that this will be included in HTA decision making and subsequently rewarded accordingly.

Additionally, this evidence can take a longer time to collect, often after the launch of the treatment. **But the formal HTA process in most countries generally does not allow for a full renegotiation of the overall value based on post-launch evidence.**

There are some exceptions where HTAs did recognize patient experience and have considered it during decision making. For example, in CNS diseases (in particular, Alzheimer's and depression), HTAs do value an increase in patient convenience as an important additional benefit. This is because the unmet need in these diseases is framed in terms of lack of ease of use. A direct relation with that and the patient's wellbeing is often drawn. In UK and Sweden, quality of life measures are incorporated into Quality Adjusted Life-Years (QALY) measures[3]. Similarly, quality of life measures are accepted by some HTAs (such as Germany) and discussed during HTA decision making but this has generally been the case in Oncology due to the end-of-life nature of the diseases. This suggests that HTAs are willing to accept a broader set of values in some cases or countries. However, such examples are rare, and it remains unclear if there is a systematic approach to valuing the benefits of improvements in experience.

3 But they may not capture broader experiential quality of life

Patients association groups also believe that a lack of substantial patient/patient representative involvement in HTA decision making is a contributing factor to the lack of inclusion of these values. In countries such as Italy and Spain, patient representatives are rarely involved in drug assessments. Patient representatives believe that the values important to them are not always reflected in HTA discussions. In countries such as Sweden, UK and Germany, patient representatives are included in drug assessments, but they feel that patient representatives are, at times, not appropriately trained to engage in these discussions to the fullest level. As a result, the patient relevant experience aspect of Person-Centered Therapeutic Innovations is under-recognised in the current environment.

Figure 11: Perceptions on User Experience and Current Pricing System (1 is Not All Agree, 3 is Somewhat Agree, 5 is Strongly Agree)

Question: Reflecting our discussion so far, how agreeable do you find the following statements, from [NOT AT ALL AGREED] / [SOMEWHAT AGREED] / [MORE OR LESS AGREED] / [FULLY AGREED]? Please elaborate in detail.

Statement 1: Usage experience related product value is **under-valued** in HTA and P&R process currently

Statement 2: Usage experience related value **should** be more integrated in the HTA and P&R process

Source: Stakeholder interviews (n=27)

Exhibit 2: Quotes from Stakeholders on User Experience Value Inclusion in HTA

"The outcomes are not clear to us and as long as that is the case, it is very hard to consider these benefits in the HTA. Unless they are improving the efficacy or saving costs, we cannot include them." **- Payer**

"I completely believe that the HTA process undervalues the patient centered aspects of a drug but we are very far away from having that discussion." **- Patient Representative**

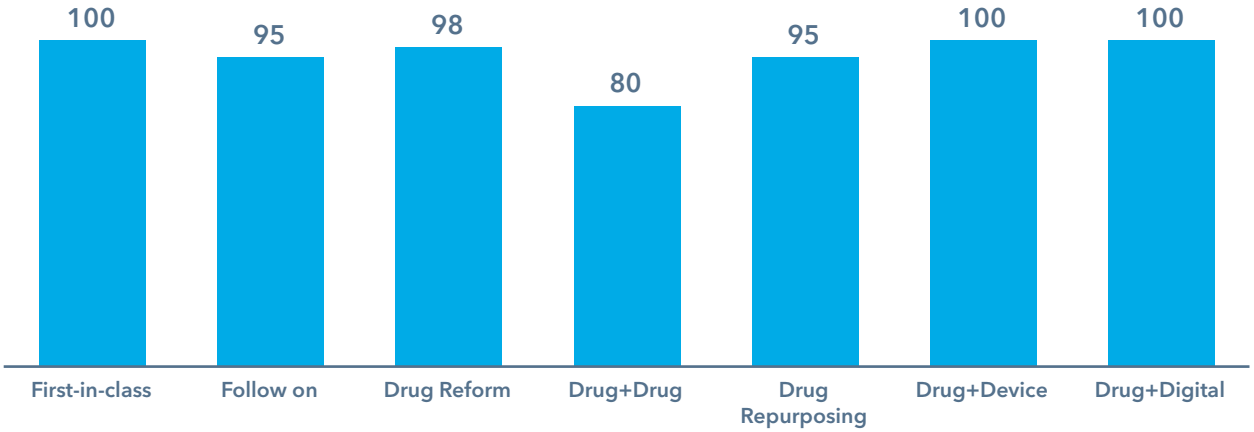
Negative HTA decisions also negatively impact pricing and reimbursement decisions for Person-Centered Therapeutic Innovations in countries with separate HTA and pricing decision-making

A pricing and reimbursement decision generally follows the HTA decisions[4] in countries that conduct HTAs and these negotiations are mostly conducted by separate parties from the ones that conducted the HTA (e.g. GKV in Germany and CEPS in France). This section explores the pricing and reimbursement decision making and the perception of payers regarding the achievable price of Person-Centered Therapeutic Innovations across all types of countries, i.e. those that have a separate HTA process and those where the pricing and reimbursement takes places simultaneously with assessments. It then looks at the list prices of these innovations vs. first-in-class.

There is an expectation that products which are not first-in-class will be priced at a lower level compared to the first-in-class (Figure 12). At best, payers noted that Person-Centered Therapeutic Innovations can achieve a similar price as first-in-class but generally the expectation is a lower price. For example, in France, a product receiving ASMR V is generally expected to launch at a minimum of a 10% discount to existing comparators. The only exceptions seem to be the UK and Sweden where payers were occasionally willing to accept a small premium over first-in-class if cost savings due to Person-Centered Therapeutic Innovations could be demonstrated at launch.

Figure 12: Price comparisons across Person-Centered Therapeutic Innovations product types vs. first-in-class (based on hypothetical exercise during the interview)

Question: Use average price of a first-in-class product as reference, i.e. at 100, based on the average products in each other product type, what do you feel is the price achieved?
Note, this can be above 100. Please explain the reasons.

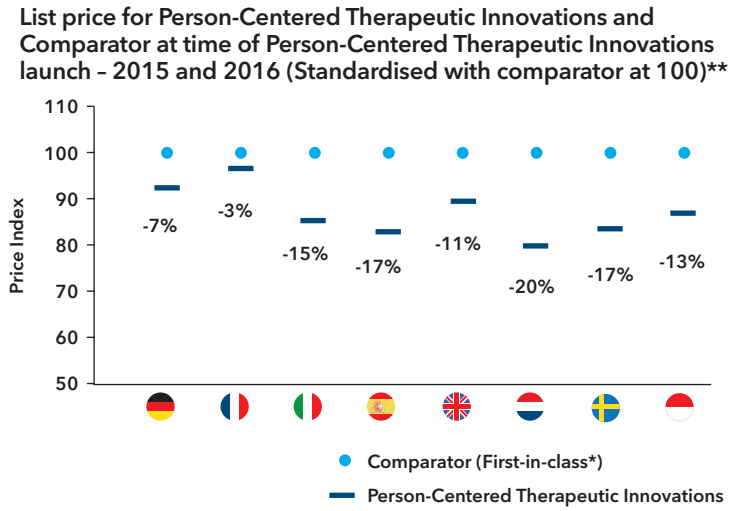


Notes: This is an average number, variations existed across countries. In particular, in Drug+Drug combinations, which saw substantial variation.

This pricing trend is also reflected, in reality, in list price data that was assessed for Person-Centered Therapeutic Innovations launching in 2015 and 2016 in disease areas in-scope (Figure 13). On average, the list price for Person-Centered Therapeutic Innovations is consistently lower than that of first-in-class (or appropriate comparators). These findings should be viewed as directional as the list price may not fully represent the price actually paid by the healthcare system due to rebates, discounts, clawbacks etc.

4 Although in some cases, there is no clear distinction between the two sets of discussions.

Figure 13: Ex-manufacturer list price per day (EUR) for comparator and Person-Centered Therapeutic Innovations (Jan 2015- Dec 2016) – Combined excludes CNS (Standardised on a price index)*



**Note: This chart shows the average price difference between the Person-Centered Therapeutic Innovations and the comparator. It has been indexed to 100 to show the difference. Launch is considered date of first sales in IQVIA MIDAS database. Prices here are compared when Person-Centered Therapeutic Innovations launched.*

Calculations do not take into consideration national and/or sub-national discounts, rebates, clawbacks etc. implemented. The analysis should be seen as directional.

In case of follow-on, the comparator is the First-in-Class product; in case of drug+drug, the price comparator is the sum of the two individual drug prices (if either of the two drugs was not on the market, it is another drug+drug)

CNS is excluded as a number of comparator prices were unclear as the comparators launched >10 years before the new product

Source: IQVIA Pricing Insights, cross checked with IQVIA MIDAS data

In some countries (such as Italy), Person-Centered Therapeutic Innovations may not be subject to HTAs and thus, their full set of benefits are not evaluated leading to access decisions being made purely on prices. Additionally, payers often do not take long term cost savings that may be offered by Person-Centered Therapeutic Innovations into consideration. The impact of direct and indirect benefits of these values on the evaluation process is also limited. For instance, in most countries P&R systems do not take into account broader societal benefits (such as reduction in absence from work).

Less positive HTA decisions, leading to unfavourable pricing and reimbursement decisions for Person-Centered Therapeutic Innovations can adversely impact final patient access

In this section, patient access is explored in terms of whether the patient is able to receive the therapy and the level of market share that a product was able to gain.

Firstly, in many countries a negative HTA decision has direct consequences on whether a therapy is reimbursed. If not reimbursed, patients could be denied access to therapies which have relevant values. As seen in Figure 9, about 25% of Person-Centered Therapeutic Innovations are not reimbursed.

Secondly, unfavourable HTA decision (such as ASMR V in France or no innovation rating in Italy) can result in lack of additional funding at the hospital level. This may result in hospitals being unable or unwilling to place a therapy on formulary which, in turn, impacts patient access. Payers noted that hospital products improving only experience are unlikely to receive favourable HTA decisions.

Some payers believe that usage experience value should be rewarded with market share instead of price. However, there are no guarantees that a product will be rewarded with market share despite potential patient preference (see Relvar Ellipta™ and Genvoya™ case studies). The reasons for this are not immediately clear from this analysis as several factors impact the uptake and market share of a product. It may be that in some cases, the HTA decisions can prevent the product from receiving additional funding thereby restricting uptake. Another reason for not being able to gain market share may be structural barriers for products that are not first-in-class to achieving a higher share thus, Person-Centered Therapeutic Innovations may end up being not rewarded on both the market share and pricing, despite having patient and user relevant value.

Additionally, the lack of inclusion of full set of benefits in the valuation of Person-Centered Therapeutic Innovations can result in a low reimbursed price. For examples, payers note addition of digital application to improve patient experience is unlikely to be discussed during P&R negotiations. Thus, the manufacturer may choose not to launch in most markets as they do not expect to be valued fully and reimbursed appropriately.

The research in this paper validates few scenarios where patient access can be impacted by HTA and pricing and reimbursement decisions. The impact of these decisions on final patient access and uptake is an area that requires further investigation to understand the possible repercussions for the final users.

RECOMMENDATIONS FOR HOLISTIC EVALUATION OF PERSON-CENTERED THERAPEUTIC INNOVATIONS

As discussed in the White paper, there are notable differences in the perception and evaluation of Person-Centered Therapeutic Innovations between payers and other health system stakeholders – while all stakeholders acknowledge the types of benefits Person-Centered Therapeutic Innovations offer, payers are far less prepared to value usage experience related benefits, compared to the final users, namely patients, physicians and providers.

It should be a health system's core mission to improve patient health and wellbeing, while ensuring that the pathway to such improvement is as efficient as possible. The disconnect between user perceived value and the health system's reception of the Person-Centered Therapeutic Innovations therefore requires reflection by all stakeholders, so that these Innovations aren't disadvantaged and disincentivised from providing relevant benefits to patients, physicians and providers, and forming an important step in the overall innovation cycle.

While the position of HTAs and payers is currently focused on outcomes assessment, regulatory bodies are paving the way for Person-Centered Therapeutic Innovations to be assessed for their full set of

benefits, including the usage experience. The FDA has published documents discussing the inclusion of patient reported outcomes and experiences in clinical trials[5]. Similarly, the EMA has published a reflection paper on the use of patient reported outcomes in clinical trials[6] to aid in designing and carrying out of clinical studies using such instruments. In this context, it seems logical that HTA bodies and payers of the future should deliberate on how to best harmonize their approach to also account for user experience relevant values more formally.

From universal coverage commitment, to institutionalisation of the HTA process, to refinement of HTA approaches, health systems across the world have demonstrated their willingness to adapt for the greater good. Authors of this White paper believe that in a world where patients are increasingly informed and societal values are evolving quickly, given underlying technological, economic and political dynamics, there is a case for the health system to better appreciate and accommodate what patients value, and by extension what their caregivers, family members, physician and providers also value.

While this White paper recognises the philosophical, methodological and implementational complexities associated with such a change, a few initiatives are proposed to help mobilise the concerned stakeholders across health eco-systems to make it happen:

- Enhance involvement of final users (i.e. patients and physicians) in HTA and pricing and reimbursement decision making
- Holistically evaluate value over a product's lifecycle and be receptive to additional data to reassess a product's value post-launch
- Better understand the value of usage experience benefits
- Explore feasibility of appropriately rewarding of Person-Centered Therapeutic Innovations with a multi-stakeholder approach

ENHANCE INVOLVEMENT OF FINAL USERS (I.E. PATIENTS AND PHYSICIANS) IN HTA AND PRICING AND REIMBURSEMENT DECISION MAKING

User involvement should increase in the HTA decision making and pricing discussions. The key stakeholders, that are finally impacted by the products, are currently not deeply involved in the decision making. Thus, there is a lack of a user and patient-centric approach to decision making. Patients/patient groups should be part of the early disease scoping process so that the unmet needs are accurately identified from a patient perspective. Additionally, patients and physician organisations should also be provided with voting rights so that their input is given the appropriate weightage, as has already been happening in some countries such as Sweden and the UK.

In this context, it is important to acknowledge that currently patients across disease areas and countries display a varying ability to engage in HTA and access discussions effectively, either due to lack of medical knowledge or understanding of how the relevant system functions. Some patient organizations are highly informed and sophisticated, whilst many individual patients and advocates lack understanding, resources and practices to have their voices heard. Similar findings have been expressed in prior research as well (Scott & Wale, 2017). In order to deliver health equitably, it is imperative that when incorporating users, especially patients, into the decision making processes, such variabilities are accounted and accommodated for, so that user inputs from across all disease areas are of comparable robustness.

5 FDA guidance on Patient Reported Outcomes; available at: https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf ; "Measuring how patients feel and function", available at: https://www.fda.gov/downloads/Drugs/NewsEvents/UCM558288.pdf

6 Reflection paper on use of PROs in clinical trials, available at: https://www.ema.europa.eu/documents/scientific-guideline/draft-reflection-paper-use-patient-reported-outcome-pro-measures-oncology-studies_en.pdf

HOLISTICALLY EVALUATE VALUE OVER A PRODUCT'S LIFECYCLE AND BE RECEPTIVE TO ADDITIONAL DATA TO REASSESS A PRODUCT'S VALUE POST-LAUNCH

Payers should assess robust post launch data (such as real-world evidence) and if these data display relevant additional value, then they should allow for renegotiation of price and HTA assessments. The argument here is straightforward, post launch data allows the product to show its full set of values while reducing payer uncertainty. Thus, there should be a mechanism to reward such data if it does demonstrate relevant added value.

BETTER UNDERSTAND THE VALUE OF USAGE EXPERIENCE BENEFITS

Direct and indirect benefits from improvements in user experience need to be identified and understood. As discussed in the examples earlier, there are several benefits for patients, physicians and providers which need to be robustly valued. The identification of such benefits will be an important first step in moving towards a complete understanding of the value of a treatment. Digital therapeutic solutions can support the development and will be an important part of capturing the usage experience related value as well as the full spectrum of associated outcome value. Big data collected through digital solutions can improve understanding of the disease and the treatment.

There are already initial studies and registries that are looking into the patient experience which may be leveraged for enhancing the understanding of usage experience. For example, the Cancer Support Community's Cancer Experience Registry collects patient preference data to gain a greater understanding of the social and emotional needs of patients and their caregivers[7]. The FDA has also started taking steps to include patient preference into their decision making by releasing a guidance document in 2016 to incorporate patient preferences (FDA 2016). A number of other smaller studies have studied the patient preference and experience aspects of drug selection (Martin H et al 2016; Mansfield, Carol et al, 2016, Taylor T et al, 2000).

This research along with the value framework in this White paper can serve as a starting point and can be further developed based on discussions with patients, patient associations and providers.

Validated measurement tools and analytics (AI, deep learning etc) need to be developed to measure and better understand these benefits. Appropriate design of these tools will require inputs from stakeholders within the health system. Academic involvement will be important at this stage to ensure the measurements are robust. Additionally, inputs from stakeholders beyond the health system, such as the general public and policy makers, will also be needed as the benefits of Person-Centered Therapeutic Innovations can be associated with broader societal value. There are projects ongoing to expand the understanding of outcomes and benefits that are relevant for patients and other users, such as International Consortium for Health Outcomes Measurement (ICHOM). Extending this work to a large set of disease areas and gaining validation through multi-stakeholder engagement will be important.

7 Cancer Support Community. Cancer Experience Registry. Available at: https://www.cancerexperienceregistry.org/about

EXPLORE FEASIBILITY OF APPROPRIATELY REWARDING THE STUDIED PERSON-CENTERED THERAPEUTIC INNOVATIONS WITH A MULTI-STAKEHOLDER APPROACH

As discussed earlier, without appropriate incentives for investing in usage experience related value measurements, manufacturers are apprehensive about funding the collection of such data. Payers have also focused mainly on the outcome benefits and not invested in collecting data on usage experience values. Thus, necessary infrastructure to appropriately understand these values is lacking. At this stage, it is not immediately clear to what extent usage experience related benefits should impact the HTA decisions and pricing and reimbursement discussions, let alone "how". Thus, a dialogue is required to discuss the requirement for a broader assessment of value and the possibility to develop the right mechanisms so that when this data does become available and showcases the benefits, it can be included in both HTA assessments and pricing and reimbursement decision making, either before, during or after a product is launched and the pricing and reimbursement decision has taken place.

The authors of this White paper recognise that the relative importance of experience versus outcomes may vary depending on the disease area and the situation in which the product is launched, for example, more inconvenience in usage may be better tolerated in light of a curative therapy, whilst psychological benefit of a therapy in a debilitating condition without a cure could prove invaluable for patients and their caregivers. In the endeavor to account for such nuances in HTA processes, multidisciplinary approaches, tapping into the latest developments in behavioral science, for example social psychology, might be required.

There is a recognition from all stakeholders that it will be a long process to ensure that therapies are valued appropriately, and that continuous innovation stays on course to deliver future generations with life-saving and quality-of-life-enchancing medical breakthroughs. Appropriate dialogue and discussion between all stakeholders will serve as a good starting point towards a broader and more holistic value assessment.

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APPENDIX

KEY STATISTICS OF PAYER ASSESSMENT REPORTS

KEY STATISTICS	
Total number of reports analysed	960
Total number of reports analysed (First-in-Class)	302
Total number of reports analysed ([Person-Centered Therapeutic Innovations])	658
Average number of reports per product (First-in-Class vs. [Person-Centered Therapeutic Innovations])	2.0 vs. 2.1
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – France	116
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Germany	87
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – UK	175
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Italy	15
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Spain	48
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Netherlands	55
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Poland	59
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Sweden	103
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Oncology	267
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Diabetes	111
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Respiratory	94
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Antiviral	88
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – CNS	65
Total number of reports analysed ([Person-Centered Therapeutic Innovations]) – Multiple Sclerosis	33

Person-Centered Therapeutic Innovations Value Framework vs. Other Value Frameworks

		Person-Centered Therapeutic Innovations Value Framework	Fastercures PPVF	ICER	ASCO	ESMO	NCCN
OUTCOMES	Clinical outcome benefit	Included	Included	Included	Included	Included	Included
	Cost benefit	Included	Included	Included	Included	Included	Included
	Efficiency benefit	Included	Discussed, not directly included	Discussed, not directly included	Not included	Not included	Not included
EXPERIENCE	Patient/family experience	Included	Included	Discussed, not directly included	Not included	Not included	Not included
	Physician experience	Included	Not included	Discussed, not directly included	Not included	Not included	Not included
	Provider experience	Included	Not included	Discussed, not directly included	Not included	Not included	Not included

Source: Fastercures, ICER, ASCO, ESMO, NCCN

PPVF: Patient Perspective Value Framework. ICER: Institute for Clinical and Economic Research, ASCO: American Society of Clinical Oncology, ESMO: European Society of Clinical Oncology, NCCN: National Comprehensive Cancer Network

RELVAR ELLIPTA™ CASE STUDY

1. CONTEXT:

Clinical trials recruit highly selected patients and efficacy data are often not translated into the same degree of effectiveness in the real world setting. For example, adherence in patients with COPD ranges from 10% to 40% in clinical practice, in contrast to the much higher rate of 70% to 90% reported in clinical trials (Bourbeau et al, 2008)

The ELLIPTA® dry powder inhaler was developed for the delivery of once-daily therapies for the treatment of asthma and chronic obstructive pulmonary disease (Grant et al, 2015)

In a 3-month placebo-controlled studies, ≥98% of patients used the Ellipta™ DPI correctly and 99% of patients found the inhaler easy/very easy-to-use and the dose counter easy/very easy to read (Riley et al, 2016)

GSK committed significant investment to generate real world evidence to further support the clinical effectiveness and safety in Asthma and COPD – Salford Lung Study (SLS)

The Salford Lung Study was a prospective, 12-month, open-label, parallel-group, randomized trial conducted in Salford and South Manchester, United Kingdom. Participants were assigned, in a 1:1 ratio, to receive one of two treatments: combination therapy with 100 µg of fluticasone furoate and 25 µg of vilanterol, administered once daily as a dry powder through an inhaler (Ellipta, GlaxoSmithKline) (the fluticasone furoate–vilanterol group); or the continuation of usual care as determined by the general practitioner (the usual-care group). For Asthma, the usual-care group consisted of treatment considered appropriate by GPs (ICS or ICS/LABA). Similarly, for COPD, the usual-care group consisted of continuation of maintenance treatment considered appropriate by GPs. (Woodcock et al, 2017) (Vestbo et al, 2016)

The SLS results became available after launch of Relvar Ellipta and have shown –

- **Asthma:** At week 24, the adjusted mean Asthma Control Test (ACT) score, which was the primary endpoint, increased by 4.4 points from baseline in patients initiated with fluticasone furoate and vilanterol, compared with 2.8 points in the usual care group (difference 1.6 [95% CI 1.3–2.0], p<0.0001). This result was consistent for the duration of the study. The number of exacerbations differed according to randomised treatment (1009 exacerbations with fluticasone furoate and vilanterol vs 1093 with usual care). Following adjustment for the logarithm of time on treatment and baseline covariates, the adjusted annual exacerbation rate between the fluticasone furoate and vilanterol group and the usual care group did not differ significantly. Pneumonia was uncommon, with no differences between groups; there was no difference in other serious

AQLQ – Asthma Quality of Life Questionnaire; Sources: Bourbeau J et al, Patient adherence in COPDThorax 2008;63:831-838; Riley JH TM et al. Correct usage, ease of use, and preference of two dry powder inhalers in patients with COPD: analysis of five phase III, randomized trials, 2016; Grant, Andrew C et al "The ELLIPTA® Dry Powder Inhaler: Design, Functionality, In Vitro Dosing Performance and Critical Task Compliance by Patients and Caregivers."; Vestbo et al, "Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice", 2016; Woodcock et al, "Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial, 2017; van der Palen et al, "A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices", 2016

CONTEXT (CONT):

adverse events between the groups. The proportion of patients who were responders based on AQLQ total score was significantly higher in the fluticasone furoate and vilanterol group than in the usual care group at week 52 (Woodcock et al, 2017)

- **COPD:** The rate of moderate or severe exacerbations was significantly lower, by 8.4% (95% confidence interval, 1.1 to 15.2), with fluticasone furoate–vilanterol therapy than with usual care (P=0.02). There was no significant difference in the annual rate of COPD-related contacts to primary or secondary care. There were no significant between-group differences in the rates of the first moderate or severe exacerbation and the first severe exacerbation in the time-to-event analyses. There were no excess serious adverse events of pneumonia in the fluticasone furoate–vilanterol group. The numbers of other serious adverse events were similar in the two groups. (Vestbo et al, 2016)

Additionally, a randomised single visit, open label, cross-over study looking at inhaler errors and preference found (van der Palen et al, 2016) –

- Fewer COPD and asthma patients made critical errors with ELLIPTA after reading the patient information leaflet vs. other devices. More asthma and COPD patients preferred ELLIPTA over the other devices. Significantly, fewer COPD patients using ELLIPTA made critical errors after reading the Patient Information Leaflet (PIL) vs other inhalers.

However, these additional evidence and values associated with Relvar Ellipta were challenging for incorporation by payers as the value of the product was already set by payers with the initial launch and there is no clear formal process for including such data in most countries

As is the case with all studies, the studies mentioned here have limitations. For this paper's purpose, we have highlighted the key evidence. Details on the limitations and trade-offs should be considered while making decisions based on this evidence. For more details, please refer to the publications listed in the sources.

AQLQ – Asthma Quality of Life Questionnaire; Sources: Bourbeau J et al, Patient adherence in COPDThorax 2008;63:831-838; Riley JH TM et al. Correct usage, ease of use, and preference of two dry powder inhalers in patients with COPD: analysis of five phase III, randomized trials, 2016; Grant, Andrew C et al "The ELLIPTA® Dry Powder Inhaler: Design, Functionality, In Vitro Dosing Performance and Critical Task Compliance by Patients and Caregivers."; Vestbo et al, "Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice", 2016; Woodcock et al, "Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial, 2017; van der Palen et al, "A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices", 2016

2. INTRODUCTION: RELVAR ELLIPTA™ IS THE FIRST ONCE-DAILY INHALED ICS/LABA AND RECEIVED EMA APPROVAL IN 2013

SUMMARY OF PRODUCT

Molecule: Fluticasone furoate (FF)/Vilanterol; FF is a steroid that reduces inflammation in the body. FF was only available as a nasal spray previously; Vilanterol is a new bronchodilator that relaxes muscles in the airways

Posology: One puff once daily; 92/22 µg (Asthma and COPD), 184/22 µg (Asthma)

Manufacturer & EMA approval year: GSK, 2013

VALUE PROPOSITION

- Relvar Ellipta™ is designed to provide **once daily administration** as well as **reduce common inhaler preparation errors** and enhance usability (reliable dosing and good lung deposition) in patients with asthma or COPD. (Svedsater et al, 2013)
- **Vilanterol** is the GSK's **new chemical entity** with long duration of action, which enables once daily dosing
- Its **3 step use system** enables simple inhaler preparation and is easy to use (Svedsater et al, 2013) (Riley et al, 2016)
- It contains a **dose indicator,** telling the patient how many puffs remain

CLINICAL OUTCOMES

In COPD, Relvar Ellipta demonstrated better efficacy vis-à-vis single molecule inhaler in reducing exacerbations and improving lung function (Dransfield et al, 2013)

In Asthma, Relvar Ellipta 92/22mg was shown to be superior to FF in reduction in exacerbations and improvements in symptom control. Relvar Ellipta 184/22mg was superior to fluticasone propionate and FF in lung function and symptom control (O'Byrne et al, 2014)

Sources: EMA public assessment & Summary of Product characteristics, GSK website, Riley JH TM et al. Correct usage, ease of use, and preference of two dry powder inhalers in patients with COPD: analysis of five phase III, randomized trials O'Byrne PM et al. Efficacy and safety of once-daily fluticasone furoate 50 mcg in adults with persistent asthma: a 12-week randomized trial. Respir Res. 2014;15:88–97, Svedsater H et al. BMC Pulm Med 2013;13:72.; Dransfield et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials, 2013)

3. PAYERS DID NOT CONSIDER THE ONCE DAILY DOSING AND ASSOCIATED CONVENIENCE DURING THEIR HTA DISCUSSIONS

Country	Agency	Decision Date	Decision	Rationale for Reimbursement	Comment on once daily dosing
	ZIN	Mar 2014	Y-cluster	Therapeutic value	Whether the difference in frequency of administration leads to differences in beneficial effects and/or adverse effects has not been proven yet.
	SMC	Mar 2014	Reimbursed COPD	Cost minimisation	Once daily may be more acceptable vs twice daily to the patient. However the double-blind design of the studies did not allow this to be assessed.
	SMC	May 2014	Reimbursed Asthma	Cost minimisation	
	AWMSG	May 2014	Reimbursed COPD	Cost minimisation	Relvar Ellipta™ (once daily) may be considered a more convenient treatment. Unclear if this factored into decision making.
	AWMSG	Jul 2014	Reimbursed Asthma	Cost minimisation	
	TLV	Jun 2014	Reimbursed	–	There is an additional value in terms of ease of use that they could not estimate and thus failed to incorporate into the analysis.
	HAS	Dec 2014	Reimbursed with restriction; **SMR: moderate** for COPD, **insufficient** for Asthma **ASMR: V** for COPD, The Commission gave an unfavourable opinion for Asthma initially but revised it to ASMR V in 2018 based on new evidence	Clinical benefit	No comment on ease of use through once daily
	AEMPS	Mar 2015	Negative (Although AEMPS issued negative statement, national access was obtained)	–	Despite a theoretical improvement in therapeutic adherence, it has not been proven yet.

Reimbursed	With restrictions	Negative

Sources: IQVIA HTA Accelerator, Payer agency websites

4. KEY TAKEAWAYS

PRODUCT SUMMARY

Relvar Ellipta™ came to market as a combination of an existing ICS combined with a new active ingredient of LABA enabling first once-daily inhaler in the market. It offers an easy to use device. Its clinical outcomes are similar to other ICS/LABA.

KEY TAKEAWAYS

1. Despite Relvar Ellipta™ proposed added benefits to patients, these value propositions were not recognised at time of launch
2. GSK committed to further investment to generate additional real world evidence and have since published additional evidence
3. Since launch, additional evidence showed:

- Salford lung study
  - » Asthma: 4.4 point increase in ACT from baseline vs 2.8 increase in usual care group; proportion of patients who were responders based on AQLQ total score significantly higher than in usual care group
  - » COPD: Rate of moderate or severe exacerbations lower by 8.4% vs. usual care
- Van der Palen et al, 2016:
  - » Fewer critical errors vs other devices after reading PIL

4. Incorporating such additional evidence post launch is challenging in most countries as there is no formal process for re-evaluation post launch

Sources: Bourbeau J et al, Patient adherence in COPDThorax 2008;63:831-838; Riley JH TM et al,. Correct usage, ease of use, and preference of two dry powder inhalers in patients with COPD: analysis of five phase III, randomized trials, 2016; Grant, Andrew C et al "The ELLIPTA® Dry Powder Inhaler: Design, Functionality, In Vitro Dosing Performance and Critical Task Compliance by Patients and Caregivers."; Vestbo et al, "Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice", 2016; Woodcock et al, "Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial, 2017; van der Palen et al, "A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices", 2016

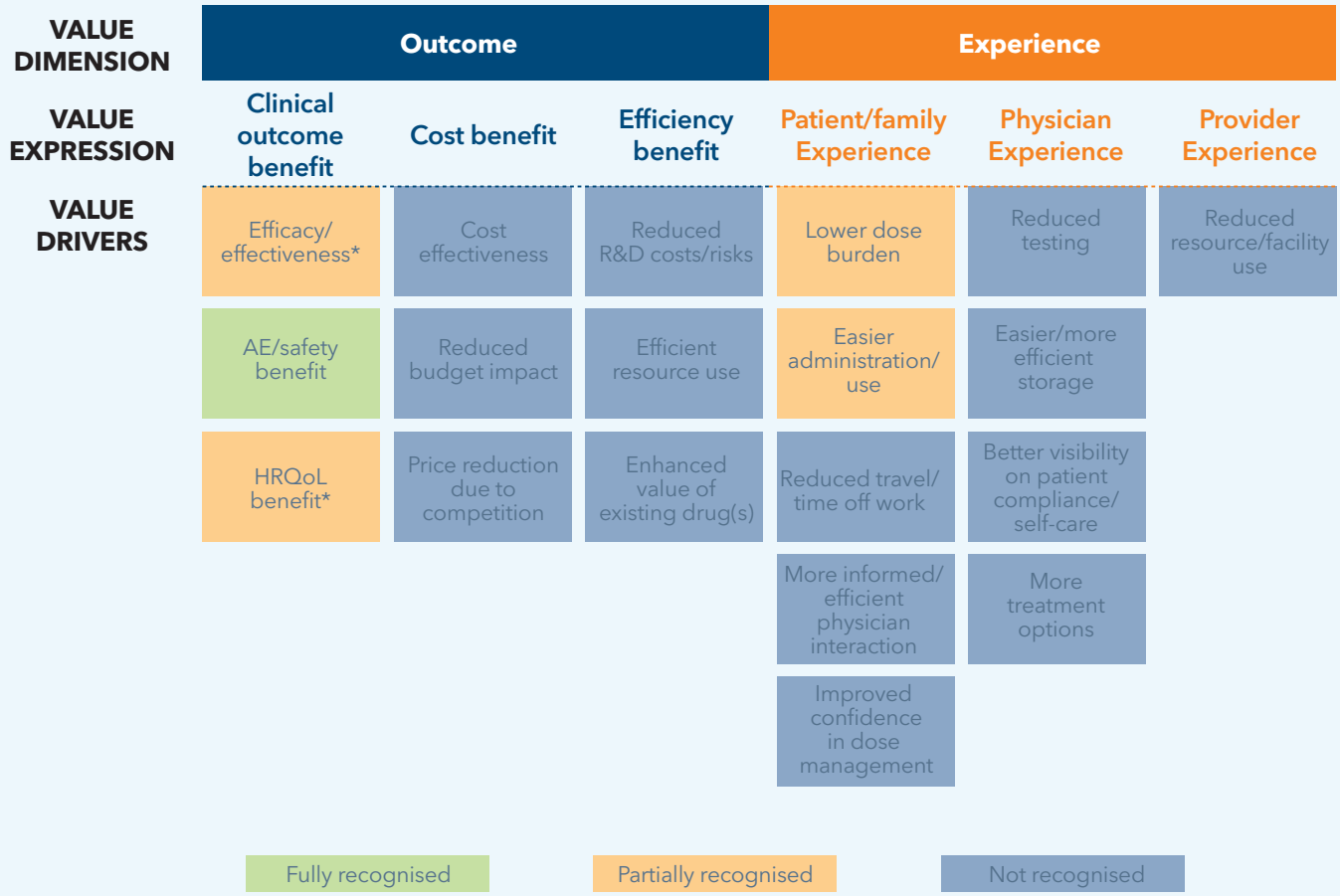
5. VALUE PROPOSITIONS BY RELVAR ELLIPTA™ ARE HIGHLIGHTED IN GREEN; THESE VALUE PROPOSITIONS INCLUDE DATA FROM RCTs AND RWE

VALUE DIMENSION	Outcome			Experience		
VALUE EXPRESSION	**Clinical outcome benefit**	**Cost benefit**	**Efficiency benefit**	**Patient/family Experience**	**Physician Experience**	**Provider Experience**
VALUE DRIVERS	Efficacy/ effectiveness*	Cost effectiveness	Reduced R&D costs/risks	Lower dose burden	Reduced testing	Reduced resource/facility use
	AE/safety benefit	Reduced budget impact	Efficient resource use	Easier administration/ use	Easier/more efficient storage	
	HRQoL benefit*	Price reduction due to competition	Enhanced value of existing drug(s)	Reduced travel/ time off work	Better visibility on patient compliance/ self-care	
				More informed/ efficient physician interaction	More treatment options	
				Improved confidence in dose management		

Key Value Proposition | Not mentioned but value provided | Not Proposed

**Note: Efficacy and Effectiveness, and HRQoL includes data from pivotal trials conducted vs. single molecules and real world evidence from Salford Lung Study*

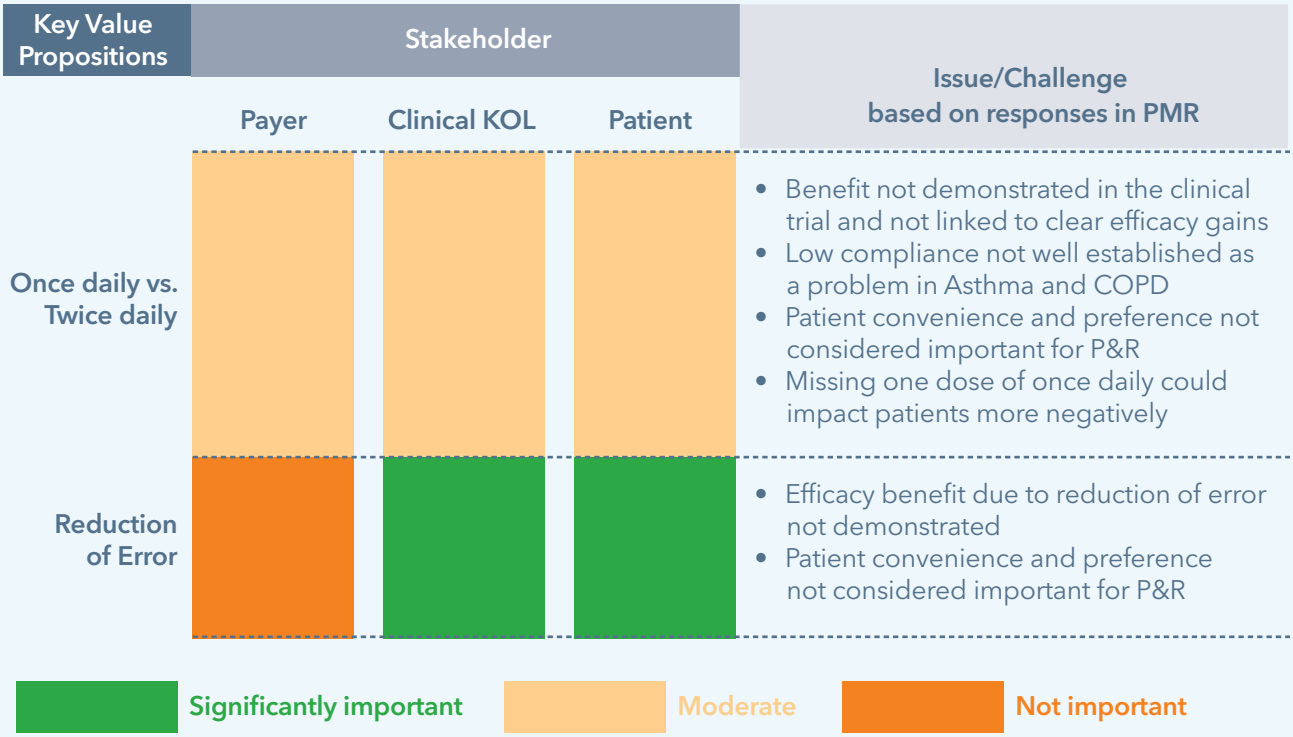
6. OUT OF THESE VALUE DRIVERS, PAYERS ONLY RECOGNISED THOSE IN GREEN



Value recognition varied across countries

**Note: Efficacy and Effectiveness, and HRQoL includes data from pivotal trials conducted vs. single molecules and real world evidence from Salford Lung Study*

7. STAKEHOLDERS' PERCEPTION ON VALUE DRIVERS DURING THE INTERVIEWS: EASE OF USE AND REDUCED DOSE BURDEN WERE KEY BENEFITS FOR PATIENTS BUT PAYERS REQUIRED LINKS TO EFFICACY MEASURES TO VIEW THEM AS RELEVANT



Source: PMR (n=27)

GENVOYA™ CASE STUDY

1. INTRODUCTION: GENVOYA PROPOSED IMPORTANT VALUE TO PATIENTS, PHYSICIANS AND HEALTHCARE SYSTEMS THROUGH THE INNOVATION OF TENOFOVIR ALAFENAMIDE

SUMMARY OF PRODUCT

Molecule: Elvitegravir, Cobicistat, Emtricitabine and Tenofovir alafenamide; Tenofovir alafenamide is a novel NRTI which more efficiently delivers the active drug tenofovir (TFV) to target cells resulting in lower plasma concentrations

Posology: 1 tablet, once daily with food; 150 mg/ 150 mg/ 200 mg/ 10 mg

Manufacturer & Approval year: Gilead, 2015

VALUE PROPOSITION

- **High efficacy:** In clinical studies in adults, Genvoya™ has demonstrated superior efficacy for treatment-naïve and virologically suppressed patients compared with TDF-containing regimens.
- **Lower bone or renal toxicity** due to tenofovir alafenamide was recognised by physicians through adoption in major international clinical guidelines
- **Suitable/preferred for many populations:** Tenofovir alafenamide enables small amount of tenofovir taken (245 mg ➔10mg)

CLINICAL OUTCOMES

In two, double-blind, Phase III studies in treatment-naïve adults (n=1,733), Genvoya™ achieved 92% virological suppression and was non-inferior to STRIBILD at week 48 (90%; pooled analysis)

Genvoya™ exhibited statistically superior efficacy compared with patients on a TDF containing regimens at Week 48 that was maintained to Week 96

Sources: IQVIA HTA Accelerator; IQVIA MIDAS; IQVIA Xchange; MPA – Swedish Medical Products Agency, EMA, https://www.sciencedirect.com/science/article/pii/S0166354215300310

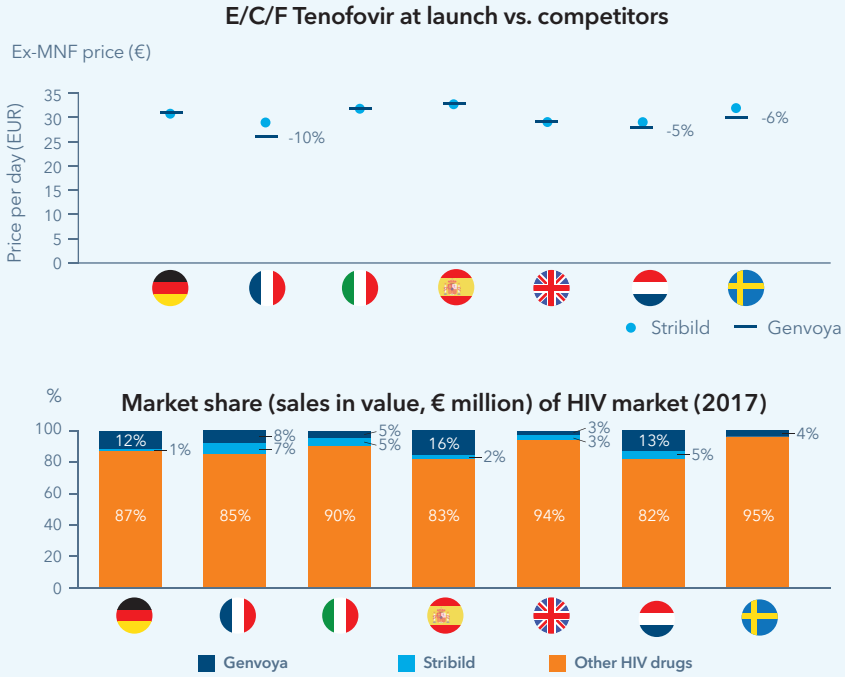
2. HTA DECISION: WHILE HTAs MENTIONED THE ADDITIONAL SAFETY BENEFITS IN THEIR ASSESSMENT, THESE BENEFITS DID NOT HAVE AN IMPACT ON DECISIONS

Country	Agency	Decision Date	Decision	Rationale for Reimbursement	Comment on added value
	ZIN	Feb 2016	Annex 1B Annex 2	High unmet need, Interchange-ability in drug class	Genvoya™ has also been shown to be effective in people with mild to moderate renal insufficiency.
	HAS	Mar 2016	SMR: Substantial ASMR:V	Clinical benefit	Genvoya™ represents a satisfactory alternative because of a similar efficiency and tolerance profile, with less alteration in the short term (48 weeks) markers biological renal
	SMC	Apr 2016		Cost effectiveness	Genvoya™ had improved laboratory markers of renal and bone safety compared with Stribild. Genvoya™ provides an alternative fixed-dose, four-drug combination, with similar antiviral efficacy to Stribild, but with lower exposure to tenofovir and therefore potentially reduced toxic renal and bone effects. It is also licensed for use in adolescents 12 years and older
	AWMSG	Jul 2016		Low budget impact	Genvoya™ maintained viral suppression and showed improved BMD and (for patients previously receiving boosted regimens) improved renal function.
	AEMPS	May 2016			The most notable difference is the new prodrug of tenofovir, tenofovir alafenamide and is found at the pharmacokinetic level which has reimbursed repercussions in terms of safety. At the bone level, safety data suggest an improvement in bone mineral density versus Stribild. Regarding renal safety, the data also suggest that TAF could induce less renal damage, including an improvement in renal damage markers
	G-BA	Jun 2016	Benefit rating: No added benefit		No mention about additional value in terms of bone or renal function (Note: Some of side effects showed a statistical difference in favour of Genvoya™, but G-BA concluded "Overall, no greater or lesser benefit from using Genvoya™ could be shown for side effects endpoint."

Reimbursed	With restrictions	Negative

Sources: IQVIA HTA Accelerator, Payer agency websites

3. GENVOYA IS PRICED AT PAR OR A SMALL DISCOUNT TO STRIBILD ACROSS COUNTRIES; IN FRANCE, IT LAUNCHED AT A 10% LOWER PRICE VS. STRIBILD DESPITE ITS ADDED VALUE PROPOSITION



Source: IQVIA Pricing Insights, cross checked with IQVIA MIDAS data, DE, FR, PL, IT (PTW), UK, SE (PTC); IQVIA internal expertise
Note: E/C/F/Tenofovir consists of Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir ; Ex-manufacturer prices

4. KEY TAKEAWAYS

PRODUCT SUMMARY

Genvoya™ is one pill with four molecules, taken once a day for HIV-1. Stribild is the originator with one pill with four molecules: the difference is Genvoya™ with "Tenofovir alafenamide (TAF)" whereas Stribild with "Tenofovir disoproxil (TDF)". Compared with TDF, TAF has >90% lower concentrations of tenofovir in the plasma, resulting in lower safety concerns and reduced need for renal tests. It was reimbursed in most markets in scope, priced at similar prices or a discount to Stribild. Since its launch, the market share of overall Descovy (emtricitabine and tenofovir alafenamide; F/TAF) which would include Genvoya™, Odefsey, Descovy in HIV antivirals has grown from 4% in 2016 to 14% in 2017.

KEY TAKEAWAYS

1. Safety related value is mentioned by some payers in reports but not a major factor driving decisions

- Most payers acknowledged the benefit in terms of the renal & bone function but decisions appear to be driven by efficacy

2. Additional value proposed is captured by payers and is not necessarily incorporated in the HTA decisions and pricing

- Genvoya™ achieved ASMR V and no added benefit and is priced at par or a small discount to Stribild across countries

3. Nonetheless, the additional value is reflected in its sales to some extent as physicians and patients value the products

- For instance, the market share of Genvoya™ increased to 9% in 2017 after its launch

5. VALUE DRIVERS OFFERED BY GENVOYA™: VALUE WAS OFFERED ON BOTH OUTCOME AND EXPERIENCE DIMENSIONS

VALUE DIMENSION	Outcome			Experience		
VALUE EXPRESSION	Clinical outcome benefit	Cost benefit	Efficiency benefit	Patient/family Experience	Physician Experience	Provider Experience
VALUE DRIVERS	Efficacy benefit	Cost effectiveness	Reduced R&D costs/risks	Lower dose burden	Reduced testing	Reduced resource/facility use
	AE/safety benefit	Reduced budget impact	Efficient resource use	Easier administration/ use	Easier/more efficient storage	
	HRQoL benefit	Price reduction due to competition	Enhanced value of existing drug(s)	Reduced travel/ time off work	Better visibility on patient compliance/ self-care	
				More informed/ efficient physician interaction	More treatment options	
				Improved confidence in dose management		

Key Value Proposition | Not mentioned but value provided | Not Proposed

Note: The cost effectiveness and reduced budget impact shown here represent proposed values in payer discussions. Exact calculations regarding these measures were not available.

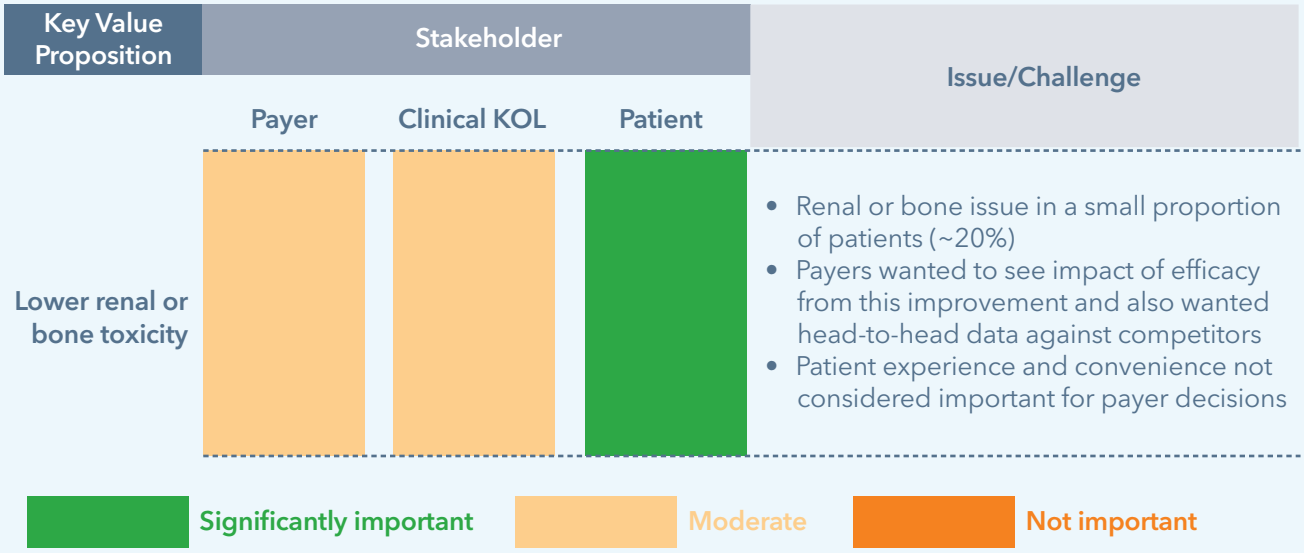
6. VALUE DRIVERS RECOGNISED BY PAYERS: HOWEVER, ONLY A FEW OUTCOME RELATED VALUES WERE RECOGNISED BY PAYERS

VALUE DIMENSION	Outcome			Experience		
VALUE EXPRESSION	Clinical outcome benefit	Cost benefit	Efficiency benefit	Patient/family Experience	Physician Experience	Provider Experience
VALUE DRIVERS	Efficacy benefit	Cost effectiveness	Reduced R&D costs/risks	Lower dose burden	Reduced testing	Reduced resource/facility use
	AE/safety benefit	Reduced budget impact	Efficient resource use	Easier administration/ use	Easier/more efficient storage	
	HRQoL benefit	Price reduction due to competition	Enhanced value of existing drug(s)	Reduced travel/ time off work	Better visibility on patient compliance/ self-care	
				More informed/ efficient physician interaction	More treatment options	
				Improved confidence in dose management		

Fully recognised | Partially recognised | Not recognised

Note: The cost effectiveness and reduced budget impact shown here represent proposed values in payer discussions. Exact calculations regarding these measures were not available.

7. STAKEHOLDERS' PERCEPTION ON VALUE DRIVERS DURING THE INTERVIEWS: PATIENTS VALUE THE IMPROVEMENTS IN SAFETY AND REDUCTION IN TESTING HIGHLY



Source: PMR (n=27)

NINLARO™ CASE STUDY

1. INTRODUCTION: NINLARO IS THE FIRST ORAL PROTEASOME INHIBITOR USED IN COMBINATION WITH TWO OTHER THERAPIES WITH SUBSTANTIAL PFS GAINS VS. ORAL DOUBLETS RD

SUMMARY OF PRODUCT

Molecule: Ixazomib; Ninlaro is a highly selective and reversible proteasome inhibitor. Ninlaro in combination with lenalidomide and dexamethasone (LenDex) is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Ninlaro is the first oral proteasome inhibitor

Posology: Orally once daily; 2.3/3/4 mg hard capsule

Manufacturer & EMA approval year: Takeda, 2016

VALUE PROPOSITION

- NINLARO is the first oral proteasome inhibitor used in combination with REVLIMID and dexamethasone (Rd) thereby offering a decrease in patient and HCP burden, lowering costs and healthcare system resource use vs hospital administered IV/SC triplets as NINLARO offers fewer clinical visits and no premedication requirement
- NINLARO provides patients who have received at least one prior therapy with an effective, sustainable and well tolerated therapeutic option. Its benefit is maintained even in difficult to treat patients.

CLINICAL OUTCOMES

In phase 3, the median progression-free survival was 20.6 months in the Ninlaro / Revlimid and dexamethasone group and 14.7 months in the placebo / Revlimid and dexamethasone group is an absolute difference 5.9 months in favour of the Ninlaro / Revlimid and dexamethasone group*.

NINLARO has a favourable toxicity profile

**Triplet regimens Kyprolis Revlimid and dexamethasone, Empliciti Revlimid and dexamethasone and Pano-Velcade reported PFS gains vs. Rd of 4.2-8.7 months*

Sources: EMA public assessment & Summary of Product characteristics , Tzogani et al, 2019, European Medicines Agency review of ixazomib (Ninlaro) for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

2. HTA DECISIONS: ONLY PAYERS IN UK ACKNOWLEDGED EASE OF USE BENEFITS

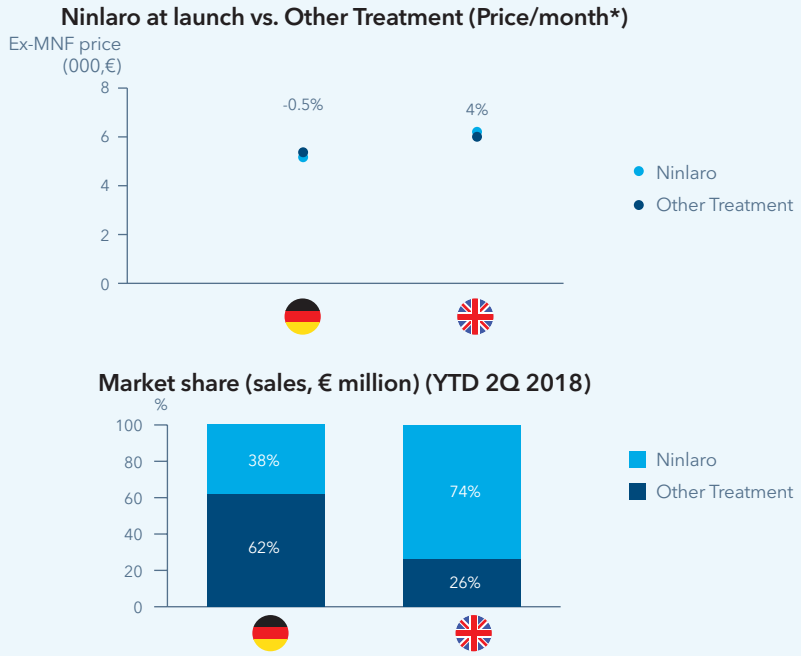
Country	Agency	Decision Date	Decision	Rationale for Reimbursement	Comment on ease of use
	HAS	Jul 2017	Reimbursed • SMR: Substantial • ASMR: V	Clinical benefit	Mode of oral administration mentioned but did not impact the ASMR ratings
	NICE	Feb 2018	Reimbursed with restriction*	Clinical benefit Cost effective	Ease of use: "The committee acknowledged that the oral administration of Ninlaro with lenalidomide and dexamethasone is a benefit, particularly for older or frail patients who find it difficult to travel to hospital for treatment."
	G-BA	Jul 2017	Benefit rating: Non-quantifiable	Clinical benefit	No comment
	TLV	May 2018	Reimbursed with restriction*	High unmet need	No comment

Reimbursed	With restrictions	Negative

**Restrictions in UK and Sweden are to match where Revlimid and dexamethasone is reimbursed in 3rd line only*

Sources: IQVIA HTA Accelerator, Payer agency websites

3. NINLARO HAS A PRICE COMPARABLE TO OTHER TREATMENT IN UK AND GERMANY (as of Aug 2018)



Note: TLV=Swedish Health authority, 45mg tablet used for Ninlaro calculations; Dosing as per label, Average BSA=1.9m2
Prices vary depending on the dosage and wastage. Exact prices are broadly in a similar range.
Source: IQVIA Pricing Insights, cross checked with IQVIA MIDAS data **Wastage is included in price for IV infusion*

Sales are taking place in Netherlands but these are not available in IQVIA database yet

4. KEY TAKEAWAYS: ALTHOUGH NINLARO ACHIEVED REIMBURSED DECISION, THE PROPOSED ADDED BENEFITS FROM ORAL DOSING WERE NOT APPRECIATED

PRODUCT SUMMARY

- Ninlaro is the first oral proteasome inhibitor for treatment of multiple myeloma. It offers clinical outcomes comparable to other treatments for multiple myeloma with increased ease of use due to oral formulation and no adverse impact on quality of life
- Ninlaro reduces the number of hospital visits for a patient
- The ease of use is particularly important for older patients and when combined with NINLARO's lower grade 3 AEs as it offers important patient experience benefits

KEY TAKEAWAYS

- The ease of administration of Ninlaro has been recognised in some HTA reports (such as the UK) but it was not the key decision rationale in most countries
- The patient convenience and reduction of burden, as well as the benefits for caregivers and treating physicians are not mentioned in payer assessments.
- The lack of valuation of these benefits can impact the full appreciation of such a product

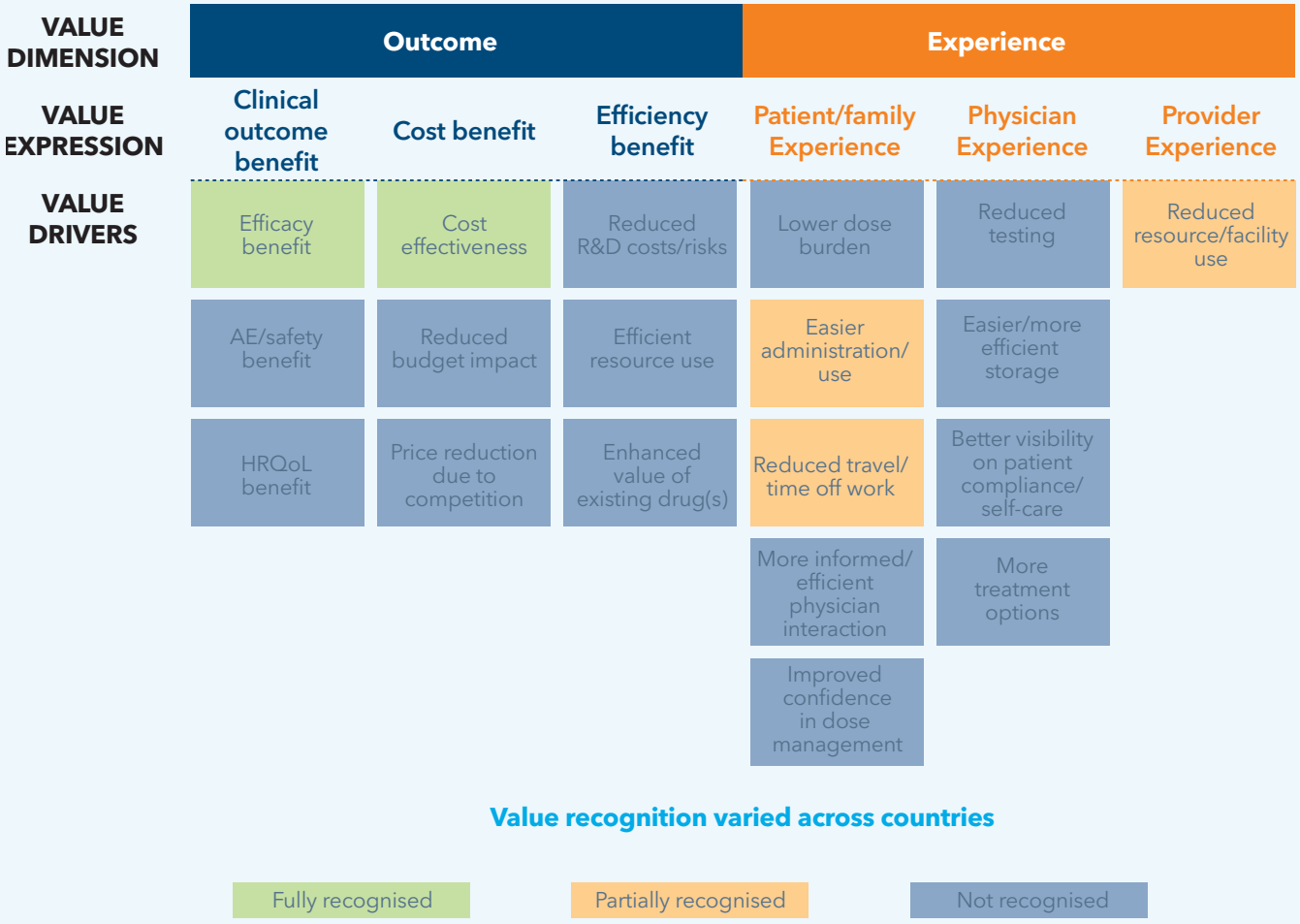
5. NINLARO PROPOSED BENEFITS ACROSS BOTH OUTCOME AND EXPERIENCE DIMENSIONS

VALUE DIMENSION	Outcome			Experience		
VALUE EXPRESSION	**Clinical outcome benefit**	**Cost benefit**	**Efficiency benefit**	**Patient/family Experience**	**Physician Experience**	**Provider Experience**
VALUE DRIVERS	Efficacy benefit	Cost effectiveness	Reduced R&D costs/risks	Lower dose burden	Reduced testing	Reduced resource/facility use
	AE/safety benefit	Reduced budget impact	Efficient resource use	Easier administration/ use	Easier/more efficient storage	
	HRQoL benefit	Price reduction due to competition	Enhanced value of existing drug(s)	Reduced travel/ time off work	Better visibility on patient compliance/ self-care	
				More informed/ efficient physician interaction	More treatment options	
				Improved confidence in dose management		

Key Value Proposition | Not mentioned but value provided | Not Proposed

Note: The cost effectiveness and reduced budget impact shown here represent proposed values in payer discussions. Exact calculations regarding these measures were not available.

6. OF THE PROPOSED BENEFITS, CLINICAL OUTCOME & COST BENEFIT WERE RECOGNISED BUT NOT THE BENEFITS IN THE EXPERIENCE DIMENSION



Note: The cost effectiveness and reduced budget impact shown here represent proposed values in payer discussions. Exact calculations regarding these measures were not available.

FLEXILEV™ CASE STUDY

1. INTRODUCTION: FLEXILEV™ PROPOSED A NUMBER OF VALUE ADDITIONS TO ENHANCE THE EXPERIENCE OF THE PATIENT AND PHYSICIANS SUCH AS SMART DOSING AND DIARY FUNCTIONS

SUMMARY OF PRODUCT

Molecule: Levidopa/Carbidopa; Levodopa is a precursor of dopamine and is given as replacement therapy in Parkinson's disease. Carbidopa is a peripheral dopa decarboxylase inhibitor

Device: MyFID, invented by Sensidose, is a smart dosing device for microtablet. Flexilev is a dosing device using a digital platform.

Posology: 50/12.5-100/25 mg of Flexilev™ every day; 5/1.25 mg (levodopa/carbidopa)

Manufacturer & Approval year: Sensidose, 2014 in Sweden

VALUE PROPOSITION

- MyFID is a **non-invasive,** first smart dosing device of tablets for Parkinson's
- **Improved adherence to treatment** because Flexilev™ is pre-programmed to deliver a certain amount of medicine at a certain time along with alarms for reminders
- **Diary function** that allows for patient to easily report symptoms and for the doctor to get a continuous picture of the disease evolution

CLINICAL OUTCOMES

In phase 1 study, the pharmacokinetics of levodopa in administering Flexilev™ are bioequivalent with conventional tablets in healthy volunteers, and that the pharmacokinetic profile is the same in healthy volunteers and in patients with advanced Parkinson's disease. There were no phase 2 or 3 study submitted to the HTA body

Sources: IQVIA HTA Accelerator; IQVIA Xchange; MPA – Swedish Medical Products Agency, EMA; http://sensidose.se/en/press-release-2/

2. PAYERS' DECISION: PAYERS IN SWEDEN DID ACKNOWLEDGE THAT FLEXILEV™ IMPROVES QOL AND IS MORE CONVENIENT BUT CLINICAL AND COST FACTORS WERE KEY DRIVERS OF DECISION MAKING

Country	Agency	Decision Date	Decision	Rationale for Reimbursement	Comment on added value
	TLV	Apr 2015	Not reimbursed	–	In the analysis, Flexilev™ appears in total as cost-saving and gives a better effect on quality of life compared to Stalevo (single pill combination with entacapone+ levodopa+carbidopa). However, the clinical effect of Flexilev™ is not shown on treated patients…therefore, there is uncertainty about whether treatment with Flexilev™ is cost effective compared to Stalevo treatment.
		May 2016	Reimbursed with restrictions Restrictions: Only in patients with advanced Parkinson's disease for whom conventional levodopa-based tablet therapy is no longer sufficient for control of motor fluctuations, and for which only levodopa-carbidopa gel or apomorphine pump delivery are possible treatment options or when inappropriate.	Cost effectiveness*	TLV estimates that treatment with Flexilev™, though, requires more maintenance times per day than invasive treatment with pump delivery of levodopa-carbidopa gel or apomorphine infusion. On the other hand, the operation of Flexilev™ appears to be less technically demanding than the handling of invasive treatments. At the same time, TLV estimates that conventional tablet treatment is more user-friendly than Flexilev™ for those patients where conventional tablets are a treatment option.

Reimbursed	With restrictions	Negative

Sources: IQVIA HTA Accelerator, Payer agency websites

**Cost effectiveness is not considered a main value add of Flexilev, the key value is improving the quality of life.*

3. KEY TAKEAWAYS: DIGITAL INNOVATION CAN IMPROVE PATIENT CONVENIENCE AND EXPERIENCE BUT PAYERS ARE UNLIKELY TO VALUE SUCH INNOVATIONS

PRODUCT SUMMARY

Flexilev™ came to market with an existing levodopa and carbidopa combined with a smart digital dosing device to provide better quality of life for patients. It provided a phase 1 clinical trial showing bioequivalence. It is marketed only in Sweden*.

KEY TAKEAWAYS

Some additional benefits for patients were acknowledged by payers in Sweden. However,

1. Overall clinical efficacy and cost effectiveness are the drivers of decision making for payers with patient and physician experience being acknowledged but not explicitly impact decision

- For instance, TLV initially granted no reimbursement due to lack of clinical efficacy data although it acknowledged Flexilev™ improves quality of life compared to comparator
- TLV did not grant reimbursement when Flexilev™ was compared with Stalevo (a single pill combination competitor at a lower price). Later, however, TLV granted reimbursement to Flexilev™ when compared with Duodopa™ (pump at a higher price) due to cost effectiveness.

2. Ex-payer responses from other countries suggest that a full appreciation of the overall value will be challenging

- Responses from ex-payers in primary research suggest the same
- Ex-payers from most countries in-scope noted that the value addition of this product would not be considered in HTA and Pricing and Reimbursement decisions and it would be expected to be priced close to the value of the constituting molecules

**Flexilev™ is only marketed in Sweden out of the countries in scope of this paper. Globally, it is also marketed in Norway and Denmark.*

4. VALUE DRIVERS OFFERED BY FLEXILEV™

VALUE DIMENSION	Outcome			Experience		
VALUE EXPRESSION	**Clinical outcome benefit**	**Cost benefit**	**Efficiency benefit**	**Patient/family Experience**	**Physician Experience**	**Provider Experience**
VALUE DRIVERS	Efficacy benefit	Cost effectiveness	Reduced R&D costs/risks	Lower dose burden	Reduced testing	Reduced resource/facility use
	AE/safety benefit	Reduced budget impact	Efficient resource use	Easier administration/ use	Easier/more efficient storage	
	HRQoL benefit	Price reduction due to competition	Enhanced value of existing drug(s)	Reduced travel/ time off work	Better visibility on patient compliance/ self-care	
				More informed/ efficient physician interaction	More treatment options	
				Improved confidence in dose management		

Key Value Proposition | Not mentioned but value provided | Not Proposed

Note: The cost effectiveness and reduced budget impact shown here represent proposed values in payer discussions. Exact calculations regarding these measures were not available.

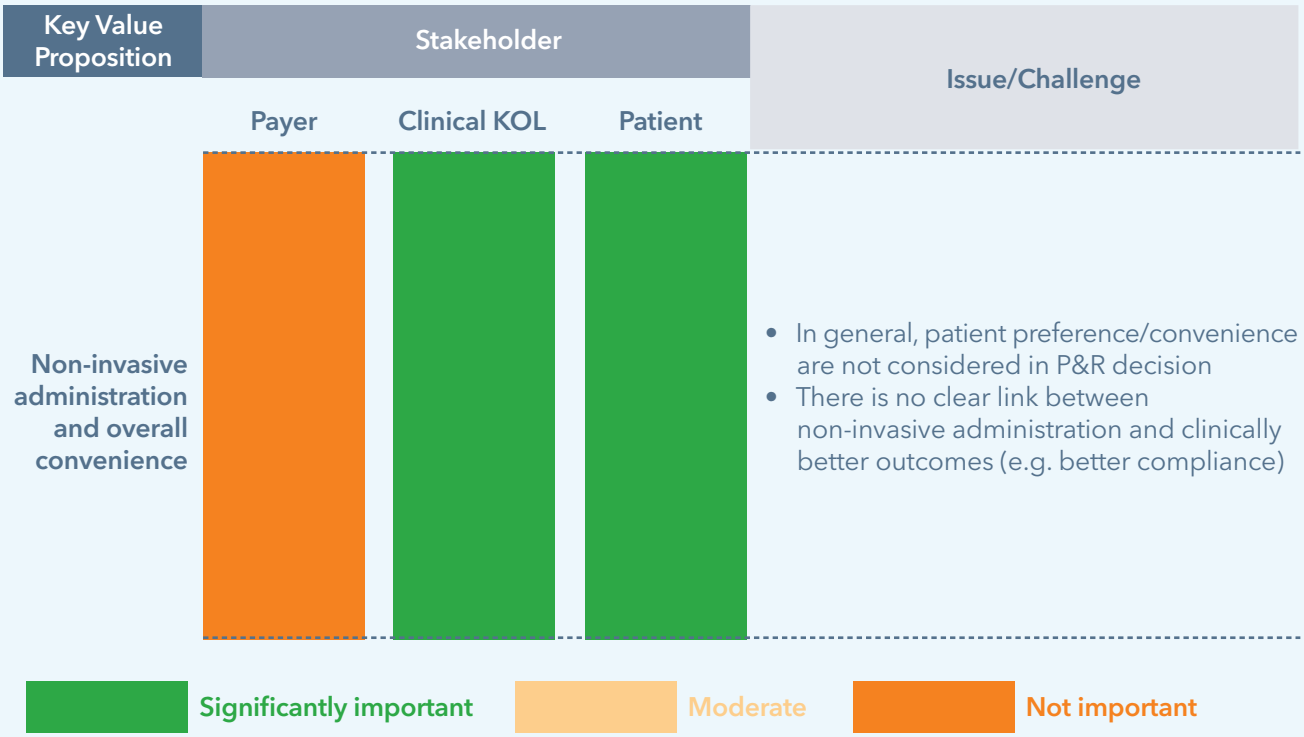
5. VALUE DRIVERS MENTIONED BY PAYERS

VALUE DIMENSION	Outcome			Experience		
VALUE EXPRESSION	**Clinical outcome benefit**	**Cost benefit**	**Efficiency benefit**	**Patient/family Experience**	**Physician Experience**	**Provider Experience**
VALUE DRIVERS	Efficacy benefit	Cost effectiveness	Reduced R&D costs/risks	Lower dose burden	Reduced testing	Reduced resource/facility use
	AE/safety benefit	Reduced budget impact	Efficient resource use	Easier administration/ use	Easier/more efficient storage	
	HRQoL benefit	Price reduction due to competition	Enhanced value of existing drug(s)	Reduced travel/ time off work	Better visibility on patient compliance/ self-care	
				More informed/ efficient physician interaction	More treatment options	
				Improved confidence in dose management		

Fully recognised | Partially recognised | Not recognised

Note: The cost effectiveness and reduced budget impact shown here represent proposed values in payer discussions. Exact calculations regarding these measures were not available.

6. STAKEHOLDERS' PERCEPTION ON VALUE DRIVERS DURING THE INTERVIEWS: PATIENTS VALUED THE CONVENIENCE OF FLEXILEV INNOVATIONS VERY HIGHLY WHILE MOST PAYERS DID NOT CONSIDER IT IMPORTANT



Source: PMR (n=27)

XIFAXAN™ CASE STUDY

1. INTRODUCTION: XIFAXAN™ WAS INITIALLY INDICATED FOR TRAVELLER'S DIARRHEA AND WAS LATER APPROVED FOR OVERT HEPATIC ENCEPHALOPATHY

SUMMARY OF PRODUCT
Molecule: Xifaxan™; Xifaxan™ is an antibiotic approved for traveller's diarrhea (Xifaxan™ 200mg). Later, it was approved for reducing the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or older (Xifaxan™ 550 mg) Indication traveller's diarrhea, hepatic encephalopathy Manufacturer & Approval year: Alfa Wassermann, Norgine, 2012 (in Europe)
VALUE PROPOSITION
• **Good efficacy** » Xifaxan™ significantly reduced the risk of an episode of hepatic encephalopathy, as compared with placebo, over a 6-month period • **Good health-related quality of life** » Xifaxan™ improves health-related quality of life in cirrhotic patients with hepatic encephalopathy: the Chronic Liver Disease Questionnaire (CLDQ) was significantly improved compared with placebo.
CLINICAL OUTCOMES
Xifaxan™ demonstrated statistically significant reduction in the risk of a breakthrough episode of overt hepatic encephalopathy compared with placebo for the intention-to-treat (ITT) population. It also demonstrated statistically significant reductions in the risks of hepatic encephalopathy-related hospital admission.

Sources: IQVIA HTA Accelerator; IQVIA MIDAS; http://sites.tufts.edu/imlib/wp-content/blogs.dir/1976/files/2014/05/Rifaximin-for-Hepatic-Encephalopathy-NEJM-2010-362-1071.pdf; https://www.ncbi.nlm.nih.gov/pubmed/21848797

2. PAYERS' DECISION: PAYERS FOCUSED ON THE CLINICAL AND COST DIMENSIONS IN THEIR HTA REPORTS

Country	Agency	Decision Date	Decision	Rationale for Reimbursement	Comment on added value
	NICE	Mar 2015	Reimbursed	Cost effective, High unmet need	The Committee noted that there was a statistically significant reduction in the risk of a breakthrough episode of overt hepatic encephalopathy compared with placebo for the intention-to-treat (ITT) population. It also noted that Xifaxan™ was associated with statistically significant reductions in the risks of hepatic encephalopathy-related hospital admission. The Committee concluded that Xifaxan™ was effective in preventing episodes of overt hepatic encephalopathy in the trial population. The Committee noted comments from consultation that treatment with Xifaxan™ would improve quality of life, prevent readmissions to hospital and reduce morbidity and carer burden.
	ZIN	Oct 2015	Not reimbursed	Non-robust economic analyses	Xifaxan™ has indeed a therapeutic added value in the prevention of the third and following episodes of manifest hepatic encephalopathy in patients ≥18 year, the pharmaco-economic analysis is insufficiently substantiated. The manufacturer insufficiently elaborated on why the healthcare perspective was chosen and not the societal perspective (which is required by the guidelines) for economic cost analysis

Reimbursed	With restrictions	Negative

Sources: IQVIA HTA Accelerator, Payer agency websites

3. KEY TAKEAWAYS

PRODUCT SUMMARY

Xifaxan™ is an antibiotic initially approved for traveller's diarrhea, and later, it was also indicated for hepatic encephalopathy. In clinical trials, it demonstrated superior efficacy and HRQoL compared with placebo. In the UK & NL, its clinical & patient values were acknowledged. However, it was not reimbursed in the NL due to insufficient economic data.

KEY TAKEAWAYS

1. Some potential patient experience values were recognised by payers, albeit it is unknown how much it impacted the decision

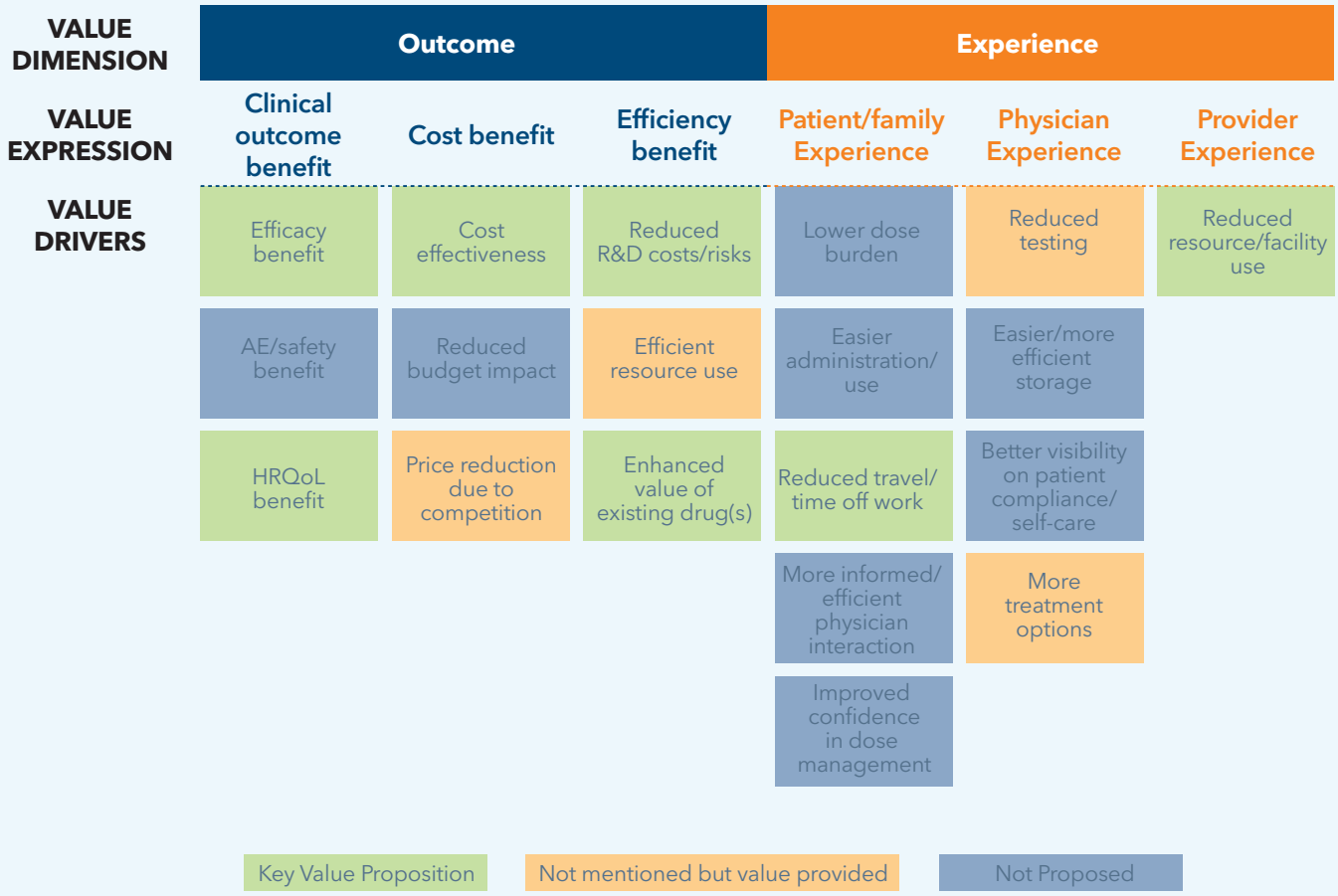
- Preventing readmissions to hospital and reducing carer burden were acknowledged in payer's review reports

2. However, outcome value especially cost benefit seems to be higher priority than experience value

- Even though ZIN acknowledged patient experience value, Xifaxan™ was not reimbursed due to not robust economic data

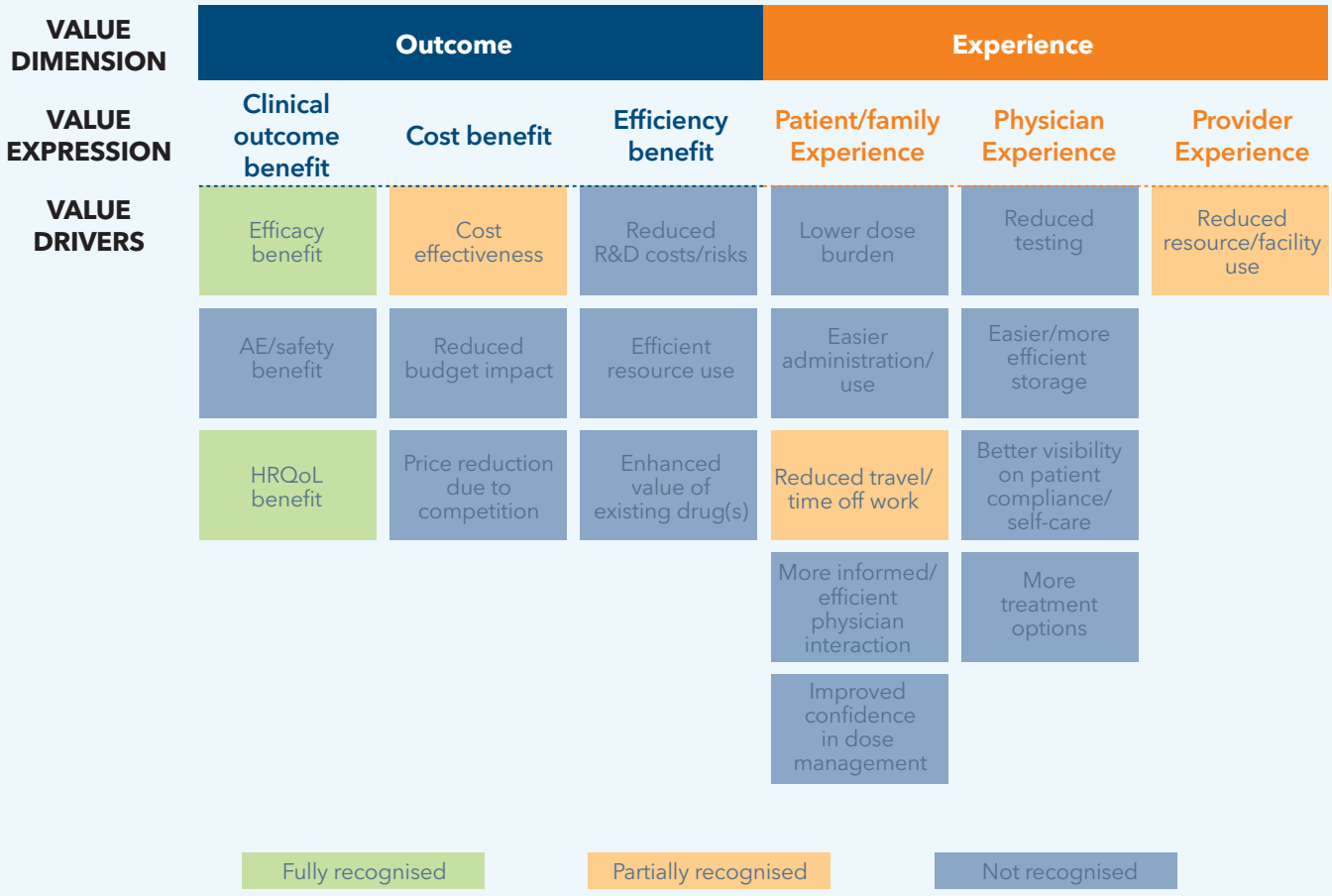
Source: IQVIA HTA Accelerator

4. VALUE DRIVERS OFFERED BY XIFAXAN™



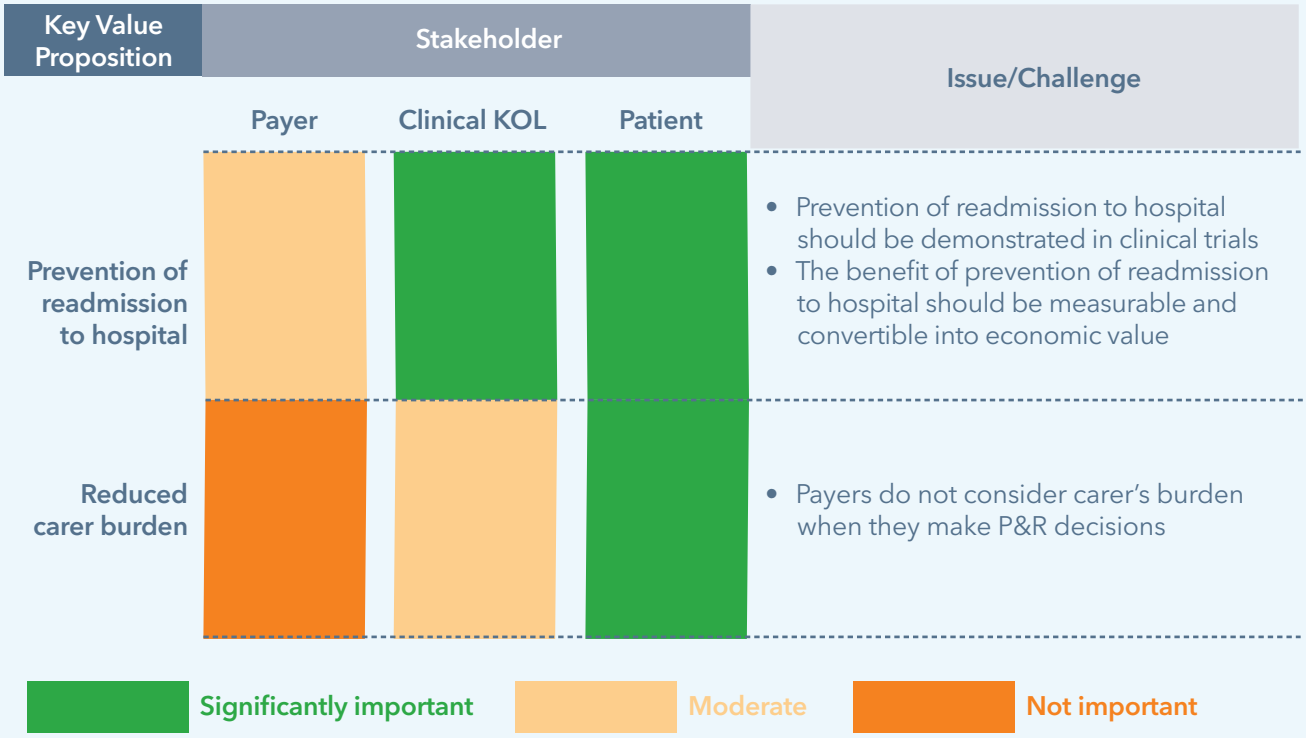
Note: The cost effectiveness and reduced budget impact shown here represent proposed values in payer discussions. Exact calculations regarding these measures were not available.

5. VALUE DRIVERS RECOGNISED BY PAYER



Note: The cost effectiveness and reduced budget impact shown here represent proposed values in payer discussions. Exact calculations regarding these measures were not available.

6. STAKEHOLDERS' PERCEPTION ON VALUE DRIVERS DURING THE INTERVIEWS: PATIENTS NOTED THE IMPORTANCE OF KEY VALUE PROPOSITIONS RELATED TO EXPERIENCE WHILE PAYERS DID NOT PERCEIVE THEM AS VERY IMPORTANT FOR THEIR DECISION MAKING



Source: PMR (n=27)

ZALDIAR™ CASE STUDY

Note: Zaldiar™ was studied as a stylised example to understand how specific values are viewed by payers and other stakeholders. Details in this case study are limited as the main purpose was to understand the perception of stakeholders to these specific value propositions. This is not meant to be fully reflective of the product's overall value.

1. INTRODUCTION [AUSTRIA]

SUMMARY OF PRODUCT

Molecule: tramadol (37.5 mg) plus paracetamol (325 mg); Zaldiar™ (another name: Ixprim™) is a fixed dose combination with two molecules above

Indication: Symptomatic treatment of moderate to severe pain not responding to peripheral analgesics used alone

Manufacturer & Approval year: Grünenthal, 2008 (decentralized procedure)*

Additional benefit from Zaldiar™ (Ixprim™)

- Better compliance due to 1 pill instead of 2 pills
- Patient convenience

HTA ASSESSMENT OUTCOME

- **Decision Date: Jun 2006**
- **Conclusion: Not Reimbursed due to disagreement on price**
- **Comment on Additional value:**

"The fixed combination offers the advantage of easier handling and lowers especially in multimorbid and geriatric patients…it is likely to achieve higher compliance than individual preparations. However, easier handling or less risk of confusion or forgetting etc. does not allow a better classification of the therapeutic benefit of the patient."

CLINICAL OUTCOMES

Zaldiar™ has superior analgesic efficacy to tramadol or paracetamol alone.

Three studies compared the efficacy of Zaldiar™ with ibuprofen 400 mg. There is no difference between Zaldiar™ and ibuprofen for 2 studies but Zaldiar™ has a lower efficacy than ibuprofen 400 mg for one study. There is no difference in efficacy between Zaldiar™ and ibuprofen 200 mg or between Zaldiar™ and 300 mg paracetamol + 30 mg codeine for chronic pain.

PRICE

Austrian Hauptverband (HVB) offered a price per tablet based on the price of generic tramadol + generic paracetamol minus 20%, these negotiations resulted in no reimbursement for the product due to lack of agreement on price.

Sources: Summary of Product characteristics, Payer HTA documents

Note: Zaldiar™ was studied as a stylised example to understand how specific values are viewed by payers and other stakeholders. Details in this case study are limited as the main purpose was to understand the perception of stakeholders to these specific value propositions. This is not meant to be fully reflective of the product's overall value.

1. INTRODUCTION [FRANCE]

SUMMARY OF PRODUCT

Molecule: tramadol (37.5 mg) plus paracetamol (325 mg); Zaldiar™ (also called Ixprim™ in FR) is a fixed dose combination of the two molecules above

Indication: Symptomatic treatment of moderate to severe pain not responding to peripheral analgesics used independently

Manufacturer & Approval year: Grünenthal, 2008 (decentralized procedure)*

Additional benefit from Zaldiar™ (Ixprim™)

- Better compliance due to 1 pill instead of 2 pills
- Patient convenience

HTA ASSESSMENT OUTCOME

- **Decision Date: Sep 2002**
- **Conclusion: Reimbursed**
- **Comment on Additional value:**

No comment on improved compliance or patient convenience

CLINICAL OUTCOMES

Zaldiar™ has superior analgesic efficacy to tramadol or paracetamol alone.

Three studies compared the efficacy of Zaldiar™ with ibuprofen 400 mg. There is no difference between Zaldiar™ and ibuprofen for 2 studies but Zaldiar™ has a lower efficacy than ibuprofen 400 mg for one study. There is no difference in efficacy between Zaldiar™ and ibuprofen 200 mg or between Zaldiar™ and 300 mg paracetamol + 30 mg codeine for chronic pain.

** Zaldiar™ (Ixprim™) was launched in France in 2003, but the marketing authorization as a decentralized procedure was approved in 2008*

Sources: Summary of Product characteristics, Payer HTA documents

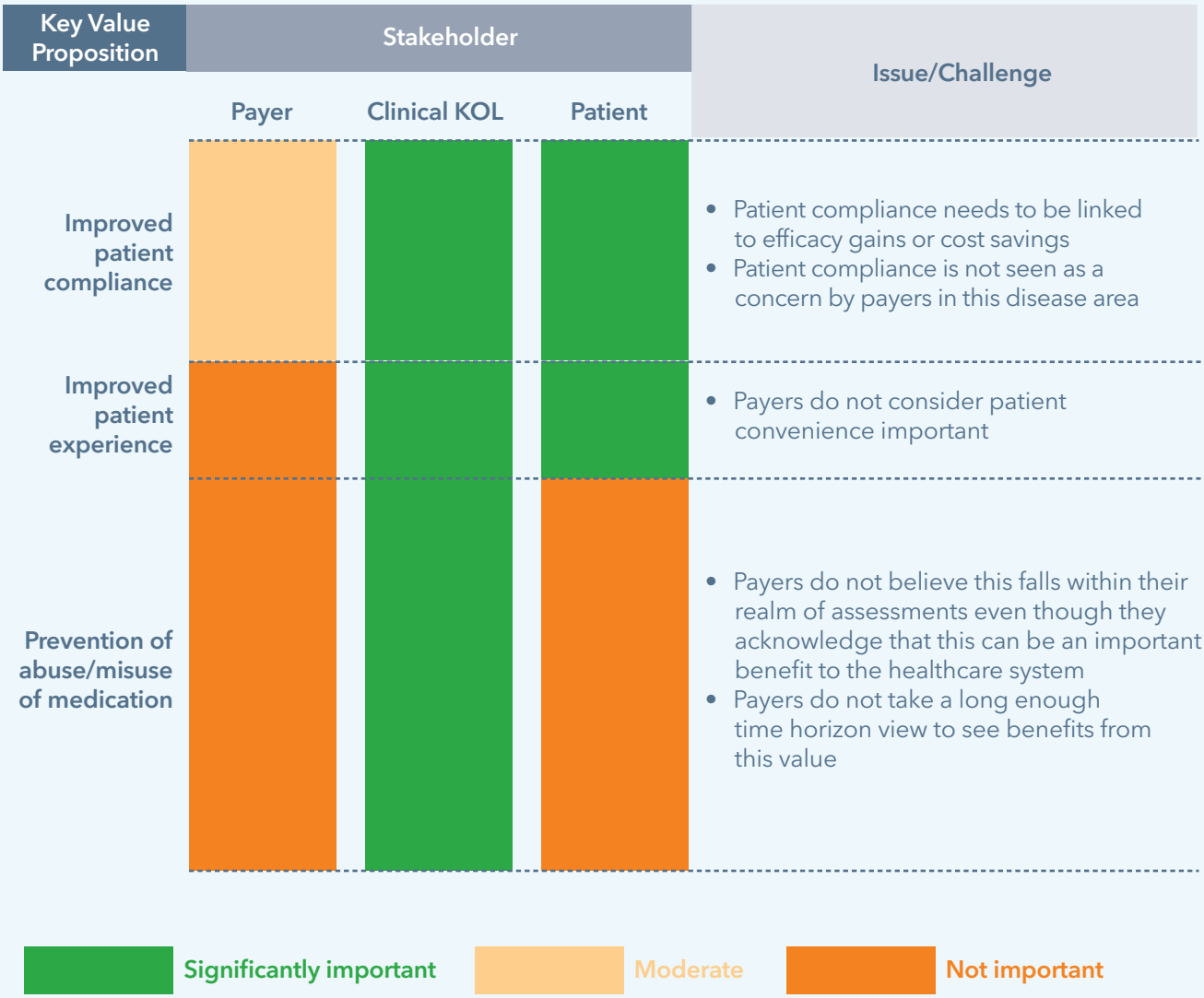
2. VALUE DRIVERS PROPOSED BY ZALDIAR™

VALUE DIMENSION	Outcome			Experience		
VALUE EXPRESSION	Clinical outcome benefit	Cost benefit	Efficiency benefit	Patient/family Experience	Physician Experience	Provider Experience
VALUE DRIVERS	Efficacy benefit	Cost effectiveness	Reduced R&D costs/risks	Lower dose burden	Reduced testing	Reduced resource/facility use
	AE/safety benefit	Reduced budget impact	Efficient resource use	Easier administration/ use	Easier/more efficient storage	
	HRQoL benefit	Price reduction due to competition	Enhanced value of existing drug(s)	Reduced travel/ time off work	Better visibility on patient compliance/ self-care	
				More informed/ efficient physician interaction	More treatment options	
				Improved confidence in dose management		

Key Value Proposition | Not mentioned but value provided | Not Proposed

Note: Zaldiar™ was studied as a stylised example to understand how specific values are viewed by payers and other stakeholders. Details in this case study are limited as the main purpose was to understand the perception of stakeholders to these specific value propositions. This is not meant to be fully reflective of the product's overall value.

3. STAKEHOLDERS' PERCEPTION ON VALUE DRIVERS DURING THE INTERVIEWS



Source: PMR (n=27)

Note: Zaldiar™ was studied as a stylised example to understand how specific values are viewed by payers and other stakeholders. Details in this case study are limited as the main purpose was to understand the perception of stakeholders to these specific value propositions. This is not meant to be fully reflective of the product's overall value.

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