

First-in-therapy products and requirements for successful HTA assessment

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Introduction

In recent history, a handful of medicines have launched as first-in-therapy products with no direct comparators while being reviewed by health technology assessment (HTA) organisations. We have attempted to document examples of these cases and explore their outcomes from HTA review. By doing so, we attempt to summarise some of the common themes for successful HTA review in the past. Looking at trial design, endpoints selected and additional factors, we attempt to draw parallels in order to determine the necessary requirements of a first-in-therapy product to support positive HTA review in the future.

Methods

An initial broad internet search was conducted to identify new products for disease areas with no previous HTA treatment. This preliminary list of products were then refined to those launching post HTA existence and likely review, specifically, within the past ten years. A wide range of disease areas and mechanisms were selected to provide as broad a view as possible across therapies. These products were then examined within the HTA databases of NICE (England and Wales), AWMSG (Wales), SMC (Scotland), NCPE (Ireland), PBAC (Australia) and CADTH/CDR (Canada). Information was then collated on clinical endpoints, HTA comparators and outcomes to provide an understanding of the requirements for positive review.

Results

Characteristics of each drug selected are noted in Table 1 below. The products identified were amifampridine for Lambert-Eaton myasthenic syndrome (LEMS), pregabalin for fibromyalgia, tetrabenazine for tardive dyskinesia (TD) and chorea of Huntington's disease, α -galactosidase for Fabry disease, vigabatrin for infantile spasms, eculizumab for paroxysmal nocturnal haemoglobinuria (PNH), and miglustat for Gaucher disease. Primary endpoints can be seen to vary substantially across products due to the varying manifestations of each disease, whereas secondary endpoints generally include functional or quality of life (QoL) measurements.

Table 1: Characteristics of selected products

Product	Disease area	Mechanism	Primary endpoint(s)	Secondary endpoint(s)
Firdapse (amifampridine)	Lambert-Eaton myasthenic syndrome (LEMS)	Voltage-dependent potassium channels	Neurological disability score (NDS), quantitative myasthenia gravis (QMG) score	
Lyrica (pregabalin)	Fibromyalgia pain	Voltage-gated calcium channel blocker	Mean pain score	Patient Global Impression of Change, Fibromyalgia Impact Questionnaire, Sleep Disturbance, Anxiety
Nitoman/Xenazine (tetrabenazine)	Tardive dyskinesia (TD) and chorea of Huntington's disease	Benzoquinolizone derivative that inhibits VMATs	Unified Huntington's Disease Rating Scale (UHDRS)	Clinical Global Impression (CGI) score
Replagal/Fabryzyme (α -galactosidase A)	Fabry disease / Anderson-Fabry disease	Enzyme replacement therapy for α -galactosidase A deficiency	Changes in liver size and urinary GAG levels	Forced vital capacity (FVC) and 6-minute walk test
Sabril (vigabatrin)	Infantile spasms	Irreversible GABA-T inhibitor	Spasm number, frequency and cessation	Other seizure activity, EEG variation, Investigator's assessment of efficacy, psychomotor assessment
Soliris (eculizumab)	PNH (paroxysmal nocturnal haemoglobinuria)	Selective terminal complement inhibitor	Reduction in hemolysis	Need for transfusion, FACIT-fatigue instrument, QoL EORTC-QLQ-C30
Zavesca	Gaucher disease, mild to moderate	Glucosylceramide synthase inhibitor	Liver volume	Haemoglobin concentration, platelet counts, bone disease

Of the products examined, several underwent review by HTA agencies as shown in Table 2. Due to a lack of alternative therapies, all but two products assessed carried out trials against placebo. As a result, the most common comparator selected by HTA agencies when undergoing review was standard care. This is due to a direct pharmaceutical comparator not being deemed as valid.

HTA outcomes can be seen to differ substantially across our products. Vigabatrin received positive recommendation due to strong trial data and inclusion of an active symptomatic comparator. A number of first-in-therapy products were rejected by HTAs in select countries for too high an incremental cost per QALY or too high an incremental cost-effectiveness ratio (ICER). Pregabalin was rejected in Canada due to concerns with trial

design and data collection despite a favourable cost per QALY. However, pregabalin was recommended for use in Australia and restricted use in Scotland.

Table 2: HTA review of selected products

Product	HTA Reviews*	Trial comparator	HTA review comparator	HTA outcome
Firdapse (amifampridine)	AWMSG	Placebo	N/A	Not recommended due to failure to submit
Lyrica (pregabalin)	SMC, PBAC, CDR	Placebo	Non-pharmaceutical management and off-label medications (gabapentin)	Recommended by PBAC and for restricted use by SMC; Not recommended by CDR
Nitoman/Xenazine (tetrabenazine)	--	Placebo	N/A	N/A
Replagal/Fabryzyme (α -galactosidase A)	NICE/AWMSG, PBAC, CDR	Placebo	Standard care	Not recommended due to high ICER
Sabril (vigabatrin)	NICE, PBAC	Placebo, hydrocortisone	Corticosteroids	Recommended
Soliris (eculizumab)	NICE, SMC, NCPE, PBAC, CDR	Placebo	Standard care (transfusions, anticoagulants, analgesics, and other interventions)	Not recommended due to high incremental cost per QALY, despite valid endpoints
Zavesca (miglustat)	PBAC, CDR	Imiglucerase	Imiglucerase and standard care	Not recommended due to high ICER and trial concerns

*Not comprehensive, but rather examples from our basket of English speaking countries

A brief summary of the overall success of selected first-in-therapy products within our specific HTA agencies of interest is provided in Table 3. Based on our products and agencies selected, the apparent success rate for first-in-therapy products differs across agencies. Furthermore, common rationale for negative recommendation also varies across agencies, ranging from a failure to submit to poor selection of outcomes, and most evidently, too high an ICER.

Table 3: Overview of HTA success rate and rationale

Characteristic	NICE/AWMSG	SMC	NCPE	PBAC	CDR
Number of first-in-therapy products reviewed	4	2	1	4	4
Number recommended*	1	1	0	2	0
Success rate*	25%	50%	0%	50%	0%
Common rationale for negative review	High ICER, failure to submit	High ICER, failure to submit	High ICER, failure to submit	High ICER	No significant benefit, poor trial design/outcomes, high ICER

*Does not include inclusion into any special access program

Conclusions and Discussion

We can conclude that based on the products assessed, first-in-therapy products do not typically receive special consideration when assessed by HTA bodies. An active comparator, use of recognised endpoints and the quality of data remain as important requirements for positive review. In cases where a disease treatment comparator is not appropriate, the HTA review comparator often included pharmaceutical interventions for symptom management. Thus, although no direct pharmaceutical comparator is used, it is interesting that HTAs often still looked at indirect pharmaceutical comparators in addition to other interventions that are part of the standard care.

Demonstrated cost-effectiveness is also required even for a novel disease area and few exceptions are made despite a lack of treatment or need for a therapy. However, this does not take into account special access programs that are available in most countries and provide access to many of these products despite a negative recommendation for general listing. Nevertheless, even these special access programs are beginning to place greater emphasis on HTA outcomes to control costs.

Therefore, earlier planning relating to cost-effectiveness research, anticipated HTA comparators and HTA views on endpoints and outcomes is necessary for manufacturers of first-in-therapy products. Working with HTA organizations and advisors to understand these implications as early as possible in product development will be extremely valuable.

It is also interesting to see the wide variety of HTA decisions for similar products and trends that are evident across HTA agencies. The choice to submit to specific agencies is often dependent on the manufacturer. Thus, looking simply at the initial success rate, it appears as though certain agencies are more strict or lenient about first-in-therapy products, namely Canada and Australia relatively speaking. While there may be insufficient examples to date to consider these findings conclusive, it may be interesting to examine in greater detail the rationale and methodology behind these decisions. Thus, we would recommend more focused studies be carried out on a country-by-country basis and for additional disease areas in order to verify these initial conclusions.