IMPACT OF ONGOING NATIONAL HEALTH TECHNOLOGY ASSESSMENT CHALLENGES ON PATIENT ACCESS TO NEW THERAPIES FOR MULTIPLE SCLEROSIS IN GERMANY AND THE UK

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Background and objective

- In recent years, health technology assessment (HTA) agencies have encountered substantial challenges when assessing the relative value of new therapies for the treatment of multiple sclerosis (MS), potentially delaying patient access to promising drugs.
- Given the methodological differences between Germany and the UK in assessing the value of new therapies, we assessed the impact of their contrasting approaches to HTA in terms of patient access to treatments for MS.

Methods

- We assessed technology appraisals for MS therapies conducted by the National Institute for Health and Care Excellence (NICE) in the UK; and the Federal Joint Committee Gemeinsamer Bundesausschuss (G-BA) in conjunction with the Institute for Quality and Efficiency in Health Care (IQWiG) since the introduction of the Pharmaceuticals Market Reorganisation Act (AMNOG) in January 2011 in Germany.
- Only technologies assessed by both NICE and G-BA/IQWiG between January 2011 and May 2015 were included in the analysis.
- Data sources comprised publicly available assessment reports from NICE (including the Evidence Review Groups [ERG]), IQWiG and G-BA.
- Each technology appraisal was assessed for therapeutic indication under consideration, target patient population and reimbursement decision.
  - Qualitative assessments of appraisal decisions in the context of overall assessment processes, evidence requirements and anticipated patient impact were also conducted for each technology.

Results

- Three therapies were assessed by both NICE and G-BA/IQWiG during the assessment period: dimethyl fumarate, fingolimod and teriflunomide.
  - During the assessment period G-BA/IQWiG also assessed fampridine and extract from *Cannabis sativa*, while NICE appraised alemtuzumab. As parallel assessments were not available in both markets for these therapies, they were excluded from the analysis.
- All three therapies were recommended by NICE as a cost-effective use of NHS resources in restricted patient populations within their licensed indications, with an agreed price discount (Table 1).
- By contrast, G-BA/IQWiG concluded that all three therapies provided no proven clinical benefit; fingolimod was determined to have minor benefit in a limited subset of patients with rapidly evolving severe relapsing–remitting MS (RES RRMS) (Table 2).
- Technology assessments in both Germany and the UK highlighted challenges in assessing clinical trial data across multiple domains, including inclusion of relevant patient populations, choice of assessment comparator and economic modelling considerations.

Patient population

- G-BA/IQWiG requires submission of clinical trial data that match the marketing authorisation. For fingolimod, this meant that only data for a small subset of patients with RES RRMS were available for consideration of added clinical benefit.
- By contrast, in the UK, NICE offers flexibility in accepting trial data that are a subset of the patient population specified in the marketing authorisation. For example, the patient population that NICE recommended as a cost-effective use of NHS resources (Table 1) was a subset of the patients explicitly specified in the fingolimod marketing authorisation.

Choice of comparator

- For NICE, choice of trial comparator(s) has a substantial impact on ERG perception of trial data, and on the likelihood of a new therapy being a cost-effective use of NHS resources.
  - For fingolimod, in 2012 the manufacturer was encouraged to use a blended comparator, including best supportive care; however, in 2014 the teriflunomide submission was criticised for using a blended comparator and the manufacturer was asked to use a pair-wise incremental analysis against each comparator, an analysis that was also used for dimethyl fumarate.
- G-BA and IQWiG mandate submission of evidence of clinical benefit versus a specified active comparator therapy, which is standard of care in Germany. Failure to provide clinical trial data that meet these criteria will result in a recommendation of "no added clinical benefit".
  - For dimethyl fumarate, there were no studies available to allow direct comparison, whereas the data for teriflunomide were limited to a specific interferon (IFN)-β only.

Table 1. Reimbursement recommendations by NICE for selected multiple sclerosis therapies between January 2011 and May 2015

	Dimethyl fumarate TA320 (August 2014)[1]	Fingolimod TA254 (April 2012)[2]	Teriflunomide TA303 (June 2014)[3]
Licensed indication at time of assessment	Treatment of adult patients with RRMS[4]	Single DMT in highly active RRMS for adult patients:[5] • with high disease activity despite treatment with at least one DMT, or • with RES RRMS	Treatment of adult patients with RRMS[6]
Drug route and dose	Oral, 120 mg *b.i.d.* (Week 1) and 240 mg *b.i.d.* thereafter	Oral, 0.5 mg *q.d.*	Oral, 14 mg *q.d.*
Patient population assessed	Adults with RRMS	Adults with highly active* or RES RRMS	Adults with RRMS
Comparator(s)	Glatiramer acetate and Rebif® (IFN-β1a)	Avonex® (IFN-β1a), best supportive care and weighted average of comparators	Glatiramer acetate
Recommendation	**Cost-effective in restricted patient population.** Patients with active RRMS† (but without highly active or RES RRMS); manufacturer provides the discount agreed in the patient access scheme	**Cost-effective in restricted patient population.** Patients with highly active RRMS and unchanged or increased relapse rate, or ongoing severe relapses compared with the previous year despite treatment with IFN-β; manufacturer provides the discount agreed in the patient access scheme	**Cost-effective in restricted patient population.** Patients with active RRMS† (but without highly active or RES RRMS); manufacturer provides the discount agreed in the patient access scheme

b.i.d., twice daily; DMT, disease-modifying therapy; IFN, interferon; NICE, National Institute for Health and Care Excellence; *q.d.*, once daily; RES, rapidly evolving severe; RRMS, relapsing–remitting multiple sclerosis; TA, technology appraisal
*Patients with highly active disease were defined as those who have failed to respond to a full and adequate treatment course (normally at least 1 year of treatment) of IFN-β. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging or at least one gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate, or ongoing severe relapses, compared with the previous year
†Normally defined as 2 clinically significant relapses in the previous 2 years

Table 2. Assessments of clinical benefit conducted by G-BA/IQWiG (since the introduction of AMNOG) for selected multiple sclerosis therapies between January 2011 and May 2015

	Dimethyl fumarate A14-14 (August 2014)[7,8]	Fingolimod A11-23 (January 2012)[9,10*]	Teriflunomide A13-38 (January 2014)[11,12]
Licensed indication at time of assessment	Treatment of adult patients with RRMS[4]	Single DMT in highly active RRMS for adult patients:[5] • with high disease activity despite treatment with at least one DMT, or • with RES RRMS	Treatment of adult patients with RRMS[6]
Drug route and dose	Oral, 120 mg *b.i.d.* (Week 1) and 240 mg *b.i.d.* thereafter	Oral, 0.5 mg *q.d.*	Oral, 14 mg *q.d.*
Patient population assessed	Adult patients with RRMS	1. Patients with highly active RRMS, full previous treatment with IFN-β 2. Patients with highly active RRMS, incomplete previous treatment with IFN-β 3. Patients with RES RRMS	Adult patients with RRMS
Comparator(s)	IFN-β1a, IFN-β1b and glatiramer acetate	1. Glatiramer acetate, IFN-β1a and IFN-β1b 2. Continuation with glatiramer acetate or IFN-β therapy with disease-modifying and authorisation pursuant optimised dosage to a reasonable cycle 3. IFN-β1a or IFN-β1b	IFN-β1a, IFN-β1b and glatiramer acetate (under consideration of the respective therapeutic indication)
IQWiG recommendation	Not proven/no clinical benefit	1. Not proven/no clinical benefit 2. Not proven/no clinical benefit 3. Hint of clinical benefit; minor/marginal additional benefit	Not proven/no clinical benefit
G-BA decision	No additional benefit	1. No additional benefit 2. No additional benefit 3. Minor/marginal additional benefit in this patient population	No additional benefit

AMNOG, Pharmaceuticals Market Reorganisation Act; *b.i.d.*, twice daily; DMT, disease-modifying therapy; G-BA, Federal Joint Committee Gemeinsamer Bundesausschuss; IFN, interferon; IQWiG, Institute for Quality and Efficiency in Health Care; *q.d.*, once daily; RES, rapidly evolving severe; RRMS, relapsing–remitting multiple sclerosis
*An additional submission for assessment for fingolimod for the management of adult patients with highly active RRMS was completed in 2014. IQWiG and G-BA both concluded that additional clinical benefit was not proven. There was no parallel submission to NICE and the 2014 assessment was, therefore, excluded from this analysis

Economic modelling

- In the UK, manufacturers are faced with substantial technical challenges when modelling treatment effect in patients with MS. Appropriate treatment sequencing, as utilised in the teriflunomide model, is typically requested despite the recognition that there is no standard UK treatment pathway.
- Use of mixed treatment comparisons (MTCs) has also come under scrutiny in the UK with NICE appearing to prefer an "all years" MTC that includes data on IFN-β trials published before 2000.
  - The initial MTC conducted for teriflunomide was based on data collected after 2000 to account for a change in the criteria used to diagnose MS (the McDonald criteria were introduced in 2001[13]); the ERG did not accept this approach and requested an additional MTC that included pre-2000 data.
- Economic modelling is not required or accepted within the current G-BA dossier template and the AMNOG process.
- Although the G-BA and IQWiG generally accept MTC data, there was only one decision by the G-BA that utilised such data on added benefit in patients with RES RRMS who were treated with fingolimod. Moreover, the model only provided a "hint" of additional clinical benefit.

Patient access

- The differing HTA and decision-making processes have influenced the MS patient populations able to access dimethyl fumarate, fingolimod and teriflunomide.
- Despite IQWiG and the G-BA finding additional benefit for only one patient subgroup for fingolimod, the drug is reimbursed across all three subgroups in the marketing authorisation, based on the pricing deal negotiated with the Federal Association of Statutory Health Insurance Funds (GKV-SV).
- In contrast, fingolimod is only available in the UK for the single subpopulation recommended by NICE (adult patients with highly active RRMS with an unchanged or increased relapse rate, or ongoing severe relapses compared with the previous year despite treatment with IFN-β).
- For both dimethyl fumarate and teriflunomide, recommendations in the UK comprise a smaller patient subpopulation than funding is available for in Germany; however, the "no additional clinical benefit" recommendation for both therapies by IQWiG in Germany had a significant impact on the price the manufacturers were able to achieve for these therapies, with discounts of 20–45% based on the German launch price.

Limitations

- Data included in the analysis were derived from publicly available sources only.

Conclusions

- Patients with MS in Germany can access all three therapies, consistent with their marketing authorisations, despite the "negative" G-BA/IQWiG appraisals.
- In the UK, patients with MS have substantially restricted access to the same therapies, partly due to the evolving methodologies and modelling requirements used by NICE to assess cost-effectiveness for MS therapies.
- Greater understanding of challenges that impact HTA decisions may facilitate earlier patient access to promising MS therapies.

References

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Disclosures

Nick Leach and Natalie Kanakam are employees of OPEN Access Consulting, Marlow, UK. Daniel Droeschel and Stefan Walzer are employees of MArS Market Access & Pricing Strategy GmbH, Weil am Rhein, Germany.

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