Technology Assessment Report (TAR) for the Appraisal of Therapies for pulmonary arterial hypertension (PAH)

GlaxoSmithKline (GSK) Comments for Consideration by the Appraisal Committee

Summary

Overall, GSK recognises that there are a number of methodological difficulties associated with a review of technologies for the treatment of PAH, such as an evidence base that is limited in terms of the small number of trials and the inadequate size of the trials themselves. Some of the complexities of this review arise because PAH is an ultra-orphan disease with small numbers of patients available for clinical trials, and no one single outcome captures the patient's whole experience of the disease. As a consequence, GSK suggest that the TAR has significant limitations, acknowledged by the Technology Assessment Group (TAG) themselves, which make it an unreliable basis for the Appraisal Committee to make any recommendations. More specifically:

- One PAH therapy cannot be compared with another in terms of cost effectiveness – relative estimates of effectiveness are not made based on similar baseline levels of risk i.e. placebo groups differ.
- Estimates of cost effectiveness are themselves not reliable as pooled estimates of effectiveness show significant levels of heterogeneity across trial populations. In addition, the incremental cost per QALYs for epoprostenol, particularly in functional class (FC) IV patients, may be over-estimated as the analysis has not included all the relevant outcomes and comparators, some of which may be expensive or of unknown cost effectiveness.
- The data do not allow the cost effectiveness of PAH therapies in specific sub-groups or as combination therapy to be explored. Absence of evidence of cost effectiveness is not the same as no evidence at all. Specifically in FC IV patients, this seems an unreasonable basis on which to prevent access for patients with a chronic, severely disabling and life-threatening disease with limited or no therapy options available.
- GSK would also urge that epoprostenol is appraised under a different process to conventional medicines and conventional orphan drugs, as PAH with a prevalence between 0.85 and 1.35 per 50,000 (17 and 27 cases per million), is an ultra-orphan disease, as acknowledged by NICE. GSK have made significant steps to make epoprostenol affordable to the NHS

Clinical effectiveness review

GSK suggest that, for the reasons detailed below, the report does not have sufficiently robust clinical effectiveness analysis to allow a decision on whether to recommend the five technologies in the treatment of PAH (Page 234 of report). Whilst GSK accepts there are difficulties of recruitment for trials in PAH, the considerable clinical heterogeneity between these trials (recognised in the report, page 166) imposes considerable limitations on the extent to which the evidence from the trials can be compared directly.

Heterogeneity in pooled trial data

- There were considerable differences in the types and mix of PAH included within and across trials, 16 trials which compared the therapies of interest with supportive therapy were deemed to be appropriate for inclusion in this report. Only two trials (epoprostenol) included a population which comprised 100% patients with primary pulmonary hypertension (PPH). One trial was conducted with 100% of patients with PAH associated with connective tissue disease (CTD) and one with 100% of patients with Eisenberger syndrome. (Table 1) The majority of the PAH trial populations were made up of a mixture of idiopathic pulmonary arterial hypertension (IPAH) (between 50 – 84%) and other types of PAH such as that associated with CTD (15-30%) and congenital heart defects.
- There were also differences in disease severity amongst patients in the epoprostenol trials. The majority of patients in the epoprostenol trials were in FC lll (65-78%) with between 17% and 26% in FC lV; only a small number, (0-9%), of patients were in FC ll. In the trials for the other therapies overall, the proportions of patients in FC ll ranged from 33-82% and the remainder were in FC lll. (Table 2) Indeed, based on baseline 6 minute walk distance (6MWD) data, the TAG concluded that the patients enrolled in the epoprostenol trials are likely to be the sickest of any of the trials in PAH (page 88). Taking this heterogeneity into account might mean that the efficacy of epoprostenol is under-estimated and/or the efficacy of the other PAH therapies is over-estimated.
- GSK note that the I^2 statistic associated with some of the pooled estimates of effectiveness indicated that there was significant heterogeneity in the data (see Table 34, pages 163-165 of report). This suggests that any

conclusions based on a direct comparison of the results of the epoprostenol trials with the more recent trials on other therapies would not be robust.

Outcomes

Survival

- The TAG note that many of the trials for the alternative therapies were neither powered nor of long enough duration to adequately measure survival (see page 162 of report). Whilst the TAR used pooled data to conclude that no significant differences in survival rates have been demonstrated between any of the therapies and supportive care (page 167 of report), GSK would like to highlight that epoprostenol is the only PAH therapy to demonstrate a reduction in mortality in a randomised controlled trial. (2)

Outcomes not reviewed

- Although one of the stated aims of the technology assessment was to examine change in FC, time to clinical deterioration (including switching of treatment and lung transplantation), lung transplantation has not been considered as a treatment option for patients (see page 61 of report). Three patients in the Barst trial underwent transplantation within the 12 week trial period.
- For patients in FC IV lung transplantation is a realistic alternative intervention and hence should be considered as an option in any assessment of treatments for PAH.

Adverse Events

- The report has identified sepsis and line infection as two of the key adverse events for consideration (see page 205 of report). GSK suggest that it should be noted in the TAR that with increasing experience of using epoprostenol the incidence of these is likely to have decreased.

Clinical practice

- The assessment examines each technology with supportive care individually. In clinical practice, therapies are often used in combination at a lower dose to achieve synergistic effect, without having to resort to the maximum dose of a monotherapy. In PAH, phophodiesterase-5-inhibiotor and endothelin receptor antagonists are likely to be used in combination. While there is no clear transition from one therapy to the next, most often, these therapies will be used in combination as the condition deteriorates.
- Whilst GSK accept that there are insufficient data to demonstrate the clinical effectiveness of combination therapy it is important to note that the findings of the TAR apply to monotherapy alone and that any recommendations arising from a consideration of this evidence base does not relate to combination therapy.

Cost effectiveness review

Outcomes

- GSK would like to highlight inconsistencies between the conclusions of the clinical effectiveness and cost effectiveness sections. In the independent assessment of cost effectiveness, the TAG have assumed the same rates of mortality for epoprostenol and iloprost in FC III patients as indicated by the probabilities in Table 44 (page 201 of the report). However, in the clinical effectiveness section, the TAG concluded that the epoprostenol trial (Barst et al.) was the only trial to show a significant survival benefit (p161-162), and although the pooled relative risk of mortality for epoprostenol was statistically insignificant, the trend was in favour of epoprostenol (page 86 of report). For iloprost the TAG concluded that no firm conclusions can be drawn for iloprost because of the small number of deaths (page 99 of report).
- The inconsistency is even more significant for the oral therapies where the reviews of clinical evidence conclude that there is no evidence of survival benefit (p161-162), but the model assumes that it is half that of epoprostenol and iloprost (0.01 or 0.011 versus 0.021); indeed for sitaxsentan and sildenafil the confidence intervals do overlap (see page 201).
- Indeed, QALY gains of 5.3-5.7 associated with the oral therapies are approximately half of those estimated for epoprostenol and Iloprost. GSK suggest that the uncertainty surrounding these estimates is significantly underestimated.
- Given the differences in the patient populations (stated in the clinical effectiveness section of this response), GSK suggest that the cost effectiveness analysis is not reliable based on pooled data with significant heterogeneity, mortality estimates unfounded by the RCT literature, and under-estimated uncertainty.

Inclusion of all appropriate outcomes and comparators

- GSK would like to highlight the inconsistencies in the choice of comparator on which the cost effectiveness results are based. All therapies are compared with supportive care alone but it is assumed that once they deteriorate to class IV that they are switched on to epoprostenol (see page 165). The implicit assumption is that epoprostenol is the standard of care for class IV patients, in which case it is unclear why this assumption is then not used for the epoprostenol comparison in class IV patients. GSK would suggest that the treatment options are consistent for both the Class III and IV model comparisons, especially given that the cost effectiveness of the oral therapies is significantly influenced by the cost of epoprostenol in the supportive care arm of the model. Indeed, the results of the current approach could over-estimate the cost effectiveness of the oral therapies and/or under-estimates that of epoprostenol.
- GSK are concerned that the cost effectiveness analysis presented in the TAR compared epoprostenol with supportive care alone and did not include other potential therapies such as transplantation or other prostanoids (beraprost or treprostinil). If epoprostenol is not recommended, particularly in FC IV patients, other unlicensed therapies not included in the scope of this appraisal and of untested cost effectiveness, will be used instead. Thus any guidance made on this basis may increase the inefficiency of PAH therapy rather than increase it.
- Transplantation was not included as a possible outcome or model state, on the basis that these are rare events (see page 208). However, these data are available in the Barst trial in which 3 out of the 81 patients enrolled had a transplant. GSK would suggest that these data are used to model this outcome in the epoprostenol cost effectiveness analysis.

Sensitivity analysis

- The range of uncertainty in the utility values used in the independent economic model (page 207) is large: the base case utilities suggest a decrement between class II and IV of 0.15, while the alternatives suggest a decrement ranging up to 0.48 (Kirsch 10 year). GSK are concerned that this uncertainty around the utilities is not adequately reflected in the model estimates.
- The non-reference case takes account of a number of variables in univariate sensitivity analysis (section 6.3.1.8, pages 208 -223 of report). However, GSK suggest that two-way sensitivity analyses are included so that the Appraisal Committee are able to see how the cost effectiveness estimates for epoprostenol change when both the reduced price for epoprostenol and different utility values are used. In addition, it is unclear in the TAR whether the cost effectiveness results are robust to variations in some of the assumptions made. The TAG understandably made a number of simplifying assumptions such as hospitalisation until death for FC IV patients on supportive care, and the dose of epoprostenol used in the first and second years of use, which are not tested (see pages 203-205 of report). It is also unclear whether uncertainty around the unit costs was considered in the probabilistic sensitivity analysis, as distributional assumptions are not explicitly stated.
- The TAR cost effectiveness was also unable to explore the cost effectiveness of different sub-groups within the PAH patient population due to limitations in the data. In the absence of this kind of analysis, it would be unreasonable to deny access to epoprostenol to patients with this chronic, severely disabling and life-threatening disease, especially in FC IV.

Ultra-Orphan disease status

- As stated in a draft discussion paper on the NICE website,(17) there is a case for not applying the normal cost effectiveness thresholds to ultra-orphan diseases in the NICE appraisal process. Ultra-orphan diseases are defined within this draft report, as having a prevalence of 1 per 50,000. PAH is mentioned within this draft report as an ultra-orphan disease, and with prevalence estimates varying between 0.85 and 1.35 per 50,000 (17 and 27 cases per million PAH), it would appear to fit the definition.
- GSK would request that the Appraisal Committee note the considerable morbidity, especially at the severe end, associated with this rare disease and would suggest therefore that as an ultra-orphan disease, the normal thresholds of cost effectiveness do not apply in this instance.
- Epoprostenol is the only licensed therapy option available to patients who are in FC IV of the disease. Without this option patients would be limited to unlicensed therapies, confinement to hospital with supportive care or transplantation. All of these options are associated with significant social and healthcare costs, and their cost effectiveness is not being assessed as part of this appraisal.
- In acknowledgement of the severity of this disease and the need for patients to have access to appropriate treatment GSK has endeavoured to ensure that epoprostenol is made available to the NHS at an affordable price.

Table 1 Differences in the types of PAH

Therapy	**Trial**	**Type of PAH (% of trial population)**							
		IPAH	CTD	CVD	AP	Non-PAH	CHD	ES	CS-P
Epoprostenol	Rubin[1]	100							
	Barst[2]	100							
	Badesch[3]		100						
Iloprost	AIR[4]	50		17	4	28			
	AIR-2[5]	63	NR	NR	NR	NR			
Bosentan	Channick[6]	84	16						
	BREATHE-1[7]	70	30						
	BREATHE-5[8]							100	
	STRIDE-2[9]	59	30				11		
Sitaxsentan	STRIDE-1[10]	53	24						24
	STRIDE-2[11]	59	30				11		
	STRIDE-4[12]	68	15				16		
Sildenafil	SUPER-1[13]	63	30						6*
	Bharani[14]	30				30		30	
	Sastry[15]	100							
	Singh[16]	50						50	

IPAH/PPH – idiopathic pulmonary arterial hypertension/primary pulmonary hypertension; CTD -Connective tissue disease or scleroderma spectrum of disease; CVD- collagen vascular disease; AP – appetite suppressant; ES- Eisenmenger syndrome; CHD – congenital heart disease; CS-P – congenital S-P shunts; * repaired congenital S-P shunts;

Table 2 Differences in functional class

Therapy	**Trial**	**Functional Class (% of trial population)**		
		Functional Class ll	Functional Class lll	Functional Class lV
Epoprostenol	Rubin[1]	9	65	26
	Barst[2]		74	26
	Badesch[3]	5	78	17
Iloprost	AIR[4]		59	41
	AIR-2[5]	33	48	19
Bosentan	Channick[6]		100	
	BREATHE-1[7]		92	8
	BREATHE-5[8]		100	
	STRIDE-2[9]	37	59	4
Sitaxsentan	STRIDE-1[10]	33	66	1
	STRIDE-2[11]	37	59	4
	STRIDE-4[12]	61	38	1
Sildenafil	SUPER-1[13]	39	58	3
	Bharani[14]	33	56	11
	Sastry[15]	82	18	
	Singh[16]	40	55	5

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