AWMSG Secretariat Assessment Report
Indacaterol acetate/glycopyrronium bromide/mometasone furoate (Enerzair® Breezhaler®) 114 micrograms/46 micrograms/136 micrograms inhalation powder, hard capsules

1.0 KEY FACTS

Assessment details	Indacaterol acetate/glycopyrronium bromide/mometasone furoate (Enerzair® Breezhaler®) is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta$_2$-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.
Current clinical practice	Asthma treatment follows a stepwise approach. At step 4 the All Wales adult asthma management and prescribing guidelines recommends a moderate maintenance dose of inhaled corticosteroid and a long acting beta agonist. For patients whose asthma is not controlled, options include increasing to a high-dose inhaled corticosteroid and long acting beta agonist or add-on therapy using tiotropium (Spiriva® Respimat®), a long acting muscarinic antagonist. Enerzair® Breezhaler® is an orally inhaled once daily, fixed-dose combination of indacaterol acetate (long acting beta agonist), glycopyrronium bromide (long acting muscarinic antagonist), and mometasone furoate (inhaled corticosteroid). Mometasone furoate is an established treatment for asthma. Indacaterol acetate and glycopyrronium bromide are recommended treatments for chronic obstructive pulmonary disease but are newly licensed for patients with asthma.
Clinical effectiveness	The company submission included two clinical trials. IRIDIUM is the pivotal phase III superiority study, measuring the efficacy of indacaterol acetate/glycopyrronium bromide/mometasone furoate versus indacaterol acetate /mometasone furoate. The study met its primary endpoint with indacaterol acetate/glycopyrronium bromide/mometasone furoate demonstrating superior improvement in trough forced expiratory volume in one second. ARGON is a phase III non-inferiority study, measuring the efficacy of indacaterol acetate/glycopyrronium bromide/mometasone furoate to salmeterol /fluticasone + tiotropium. The study met its primary end point; indacaterol acetate/glycopyrronium bromide/mometasone furoate demonstrated non-inferiority via an Asthma Quality of Life Questionnaire.
Cost-effectiveness	A cost-minimisation analysis compares indacaterol acetate/glycopyrronium bromide/mometasone furoate with

	salmeterol/fluticasone + tiotropium for maintenance treatment in adult patients (aged ≥ 18 years) with inadequately controlled asthma. The company base case suggests cost savings of £2,526 per patient over a lifetime horizon. Scenario analyses suggest cost-savings between £1,177 and £3,475, taking into account uncertainty related to model assumptions. These scenario analyses support the base-case results. Given the absence of well-designed equivalence and appropriate head-to-head trials, the use of cost-minimisation analysis is inappropriate in this instance. The model only considers differences in medication acquisition costs assuming all other resource use between arms is equal.
Budget impact	[commercial in confidence section removed]
Additional factors to consider	Enerzair® Breezhaler® is the first licensed fixed-dose combination of the three active substances for treatment of asthma. An electronic sensor is available for use with this medicine. When attached to the inhaler, it records the patient's use and sends the information to the patient's smartphone. The sensor is optional and it is not needed for using the inhaler.

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd. and an evidence search conducted by conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) on 26 January 2021[1].

2.0 BACKGROUND

2.1 Condition and clinical practice

Asthma is a chronic long-term lung disorder affecting people of all ages, in which inflammation and narrowing of the bronchial tubes leads to breathing difficulties, tightness in the chest, coughing and wheezing[2]. The condition is responsible for a large number of accident and emergency attendances and hospital admissions and results in approximately 70 deaths in Wales each year[3,4].

The diagnosis of asthma is based on history of characteristic symptom patterns and evidence of variable airflow limitation[5]. Lung function testing using spirometry includes measures of peak expiratory flow rate (PEF) and the forced expired volume in one second (FEV_1), see Glossary[5].

The aim of asthma management is risk reduction and symptom control. Management of asthma is recommended in a 'stepwise' approach to escalation or de-escalation of treatments based on patients' asthma control. For adult patients with ongoing poor control on a moderate maintenance dose of inhaled corticosteroid (ICS)/long acting $beta_2$-agonist, increasing to a trial of high-dose treatment is recommended as an option; tiotropium (Spiriva® Respimat®), a long acting muscarinic agonist, is recommended as an option for add-on therapy. Leukotriene receptor antagonist, low dose sustained-release theophylline, biologic therapy or low dose oral corticosteroids are also alternative add on therapies[6].

2.2 Medicine

Enerzair® Breezhaler® is an orally inhaled once daily, fixed-dose combination of indacaterol acetate, glycopyrronium bromide, and mometasone furoate (IND/GLY/MF). Each capsule contains 150 micrograms of indacaterol (as acetate), 50 micrograms of glycopyrronium (as bromide) and 160 micrograms of mometasone furoate. The capsule is administered using the Concept1 dry-powder inhaler, which may contain an electronic sensor that can link to a mobile application (app); the sensor and app are not required for administration of the medicinal product to the patient[7].

Indacaterol is a long acting beta2- agonist (LABA) and a partial agonist at the human beta2-adrenoceptor which acts locally in the lung as a bronchodilator. Glycopyrronium is a long-acting muscarinic receptor antagonist (LAMA) which blocks the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, dilating the airways. Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and anti-inflammatory properties[8].

Mometasone furoate is an established treatment for asthma[9]. Indacaterol acetate and glycopyrronium bromide are recommended treatments for chronic obstructive pulmonary disease but are newly licensed for patients with asthma[10].

2.3 Comparators

The comparator included in the company's submission is

- salmeterol /fluticasone + tiotropium (S/F+TIO)

2.4 Guidance and related advice

- AWMSG All Wales Adult Asthma Diagnosis and Management Guidelines (2020)[6]
- Global Initiative for Asthma. Global strategy for asthma management and prevention (2020)[5]
- National Institute for Health and Care Excellence, Asthma: diagnosis, monitoring and chronic asthma management. NG80 (2020)[11]
- British Thoracic Society/Scottish Intercollegiate Guidelines Network. SIGN 158. British guideline on the management of asthma. A national clinical guideline (2019)[12]

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of tiotropium (Spiriva® Respimat®)[13] and fluticasone furoate/vilanterol (as trifenatate) (Relvar® Ellipta®)[14] for use in asthma.

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, IND/GLY/MF (Enerzair® Breezhaler®) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

3.0 CLINICAL EFFECTIVENESS

The company submission included two phase III clinical trials. IRIDIUM[15] compared the efficacy and safety of IND/GLY/MF versus IND/MF and also included a comparison with S/F in patients with inadequately controlled asthma. ARGON[16] was a non-inferiority study comparing IND/GLY/MF to S/F + TIO. ARGON informed the cost-minimisation analysis. Only the high strength IND/GLY/MF results will be discussed in terms of efficacy and cost analysis. All IND/GLY/MF doses are taken into

consideration for the comparative safety.

Enerzair® Breezhaler® was granted marketing authorisation by the European Medicines Agency (EMA) in July 2020. Initially, the company developed two strength combinations for Enerzair® Breezhaler® which were included in the pivotal trials. The lower strength combination contained a medium dose of mometasone furoate (ICS), however only the combination with the higher ICS strength was recommended for approval by CHMP[8]; only the efficacy results of the licensed higher strength combination are discussed below.

3.1 IRIDIUM study

IRIDIUM was a 52-week, randomised, double-blind, double-dummy, parallel-group, active controlled study. Eligible patients had inadequately controlled asthma and all had been receiving either medium or high dose LABA/ICS for at least 3 months before the study[15]. The mean age was 52.2 years (standard deviation 12.7 years). In the previous 12 months, approximately 80% of the patients had experienced one asthma exacerbation, approximately 20% had two or more asthma exacerbations and less than 1% had experienced no exacerbations[15]. Patients (n= 3,092) were randomised (1:1:1:1:1) into one of five treatment arms. Patients received either IND/GLY/MF 150/50/160 micrograms delivered via Concept1 dry inhaler device, IND/MF 150/320 micrograms delivered via Concept1 dry inhaler device, S/F 50/500 micrograms delivered via Accuhaler®, lower strength IND/GLY/MF or lower strength IND/MF[15]. The efficacy of the lower strength treatments are not discussed.

The primary endpoint for IND/GLY/MF was achieved. IND/GLY/MF demonstrated significantly superior improvement in trough forced expiration volume in one second (FEV_1) at Week 26 versus IND/MF (see Table 1). This improvement in trough FEV_1 was maintained at week 52[15]. The secondary endpoint, Asthma Control Questionnaire (ACQ-7) (see Glossary) after 26 weeks was not met. Over 52 weeks, there were reductions in the number of exacerbations for IND/GLY/MF compared to IND/MF. Differences for severe exacerbations and all exacerbations were statistically significant.

The endpoints for change in FEV_1 and change in ACQ-7 were achieved for IND/GLY/MF versus S/F (see Table 1). Clinically meaningful reductions for moderate to severe and severe exacerbations were also observed for IND/GLY/MF compared with S/F [8]. This comparison is not pivotal, but was considered relevant and supportive for the proposed indication.

Table 1: Results of Iridium study[15]

	IND/GLY/MF (n= 619) vs IND/MF (n= 618)	IND/GLY/MF (n=619) vs S/F (n=618)
Primary endpoint Change in FEV_1*	65ml (95%CI: 31-99) p<0.001	119ml (95%CI: 85-154) p<0.001
Secondary endpoint Change in ACQ-7†	0.014 (95%CI: -0.066 to 0.094) p=0.73	-0.086 (95%CI: -0.165 to -0.006) p = 0.034
Ratio of annualised rate of moderate or severe exacerbations§	0.85 (95%CI: 0.68-1.04) p=0.12	0.64 (95%CI: 0.52-0.78) p<0.001
Ratio of annualised rate of severe exacerbations§	0.78 (95%CI: 0.61-1.00) p=0.05	0.58 (95%CI: 0.45-0.73) p<0.001
Ratio of annualised rate of all exacerbations ¶	0.79 (95%CI: 0.66-0.96) p=0.016	0.60 (95%CI:0.50-0.72) p<0.001

* change in trough FEV_1 from baseline to 26 weeks (primary endpoint vs IND/MF, secondary endpoint vs S/F)
† change in Asthma Control Questionnaire 7 from baseline to week 26 (a negative value constitutes an improvement)
§ exacerbation rate from baseline to week 52
¶ all (mild, moderate and severe) exacerbations from baseline to week 52
IND/GLY/MF: indacaterol acetate/glycopyrronium bromide/ mometasone furoate; S/F: salmeterol furoate/fluticasone; CI: confidence interval

3.2 ARGON study

ARGON was a randomised, partially-blinded, 24-week, parallel-group, non-inferiority, open-label active controlled study. Adults with asthma for at least six months prior to screening treated with medium or high dose ICS/ LABA and a history of at least one severe asthma exacerbation that required medical care and systemic corticosteroid treatment for at least three days in the past 12 months were included[16]. The mean age was 52.5 years (standard deviation 13.3 years). Patients were randomised (1:1:1) into one of three treatment arms: IND/GLY/MF once daily via Breezhaler® (n=476), S/F twice daily via Accuhaler® + TIO once daily via Respimat® (n=475) or lower strength IND/GLY/MF. The lower strength treatment is not licensed in the UK and its efficacy is not discussed[16].

The study met its primary objective of non-inferiority: the difference in the Asthma Quality of Life Questionnaire (AQLQ) score was non-inferior for IND/GLY/MF versus S/F + TIO (see Table 2)[16]. A higher percentage of responders achieved the minimally clinically important difference in AQLQ with IND/GLY/MF versus S/F + TIO. The improvement in the ACQ-7 score, and FEV_1 was also greater for IND/GLY/MF. No statistically significant differences were found for the reduction in rates of mild, moderate and severe, and all exacerbations, however the annualised rate of moderate exacerbations decreased by 43% (p=0.042) with IND/GLY/MF versus S/F + TIO[16].

Table 2: Results of Argon study[16]

	IND/GLY/MF (n= 476) versus S/F +TIO (n=474*)
Primary endpoint Change in AQLQ†	0.073 (95% CI:-0.027 to infinity) p< 0.001
Proportion of AQLQ responders§	Odds ratio 1.33 (95% CI: 1.03-1.70); p=0.013
ACQ-7¶	-0.124 (95 % CI: -0.216 to -0.032); p=0.004
Change in FEV_1**	0.096 litres (95%CI: 0.046-0.146), p<0.001
Ratio of annualised rate of moderate or severe exacerbations§§	0.88 (95%CI: 0.65-1.19), p=0.414
Ratio of annualised rate of severe exacerbations§§	1.14 (95%CI: 0.79-1.64), p=0.494
Ratio of annualised rate of all exacerbations¶¶	0.81 (95%CI: 0.62-1.06), p=0.123

* one patient randomised to S/F + TIO was not treated.
† least squares mean change in Asthma Quality of Life Questionnaire between baseline and 24 weeks (non inferiority margin 0.25), treatment difference is one-sided (a positive value constitutes improvement)
§ proportion of patients achieving minimally clinically important difference > 0.5 in AQLQ from baseline to 24 weeks
¶ change in Asthma Control Questionnaire 7 from baseline to week 24 (a negative value constitutes an improvement)
** least mean squares change in trough forced expiration volume in 1 second from baseline to 24 weeks
§§ exacerbation rate from baseline to week 24
¶¶ all (mild, moderate and severe) exacerbations from baseline to week 24

IND/GLY/MF: indacaterol acetate/glycopyrronium bromide/mometasone furoate; S/F +TIO: salmeterol furoate/fluticasone plus tiotropium; CI: confidence interval

3.3 Comparative safety

The safety profile of indacaterol acetate, glycopyrronium bromide and mometasone furoate as individual substances are well characterised within their licensed indications as monotherapy and double fixed dose combinations[8]. Adverse events were comparable across the treatments in the IRIDIUM study[7],the most common adverse events for IND/GLY/MF were asthma (exacerbation) (41.8%), nasopharyngitis (10.9%), upper respiratory tract infection (5.6%) and headache (4.2%)[7]. Asthma exacerbations occurred less frequently in both IND/GLY/MF arms compared to both IND/MF arms (incidence rate 52.9 v 53.2 and 55.2 v 62.3)[8]. The most common adverse event considered to be drug related was dysphonia, this had the highest incidence rate in the IND/GLY/MF arm[8]. In the ARGON study, both high- and medium-dose IND/GLY/MF had safety profiles comparable with S/F + TIO. The most frequently reported adverse events were similar to those recorded in the IRIDIUM study[16]. Serious adverse events occurred at low frequencies and were comparable in all groups[8].

3.4 AWTTC critique

- Enerzair® Breezhaler® is the first ICS/LABA/LAMA combination inhaler for the treatment of asthma being considered for use in NHS Wales; both indacaterol acetate and glycopyrronium bromide are newly licensed for patients with asthma.
- There are a number of fixed-dose ICS/LABA combination inhalers used in Wales. Treatment options for those asthma patients not adequately controlled on moderate-dose regimens include the addition of tiotropium, or an increase to high-dose ICS/LABA[6]. Whilst there is direct comparison of IND/GLY/MF versus S/F + TIO and IND/MF, no comparison to other fixed-dose ICS/LABAs were

provided by the applicant company. The company submission included a systematic literature review and a study evaluating beclometasone/formoterol + TIO was found. However, it is noted that an indirect comparison was limited by a restricted evidence network, heterogeneous study populations and a difference in study endpoints.

- EMA guidelines state that measurement of lung function parameters alone is considered insufficient for an assessment of the therapeutic effect[17]. In the pivotal IRIDIUM study the primary endpoint FEV_1 was met but the key secondary endpoint ACQ-7 did not achieve statistical significance. Effect on exacerbation is considered to be particularly important to assess clinical relevance of the treatment and a clinically relevant reduction in severe exacerbations was achieved versus IND/MF. Significant and clinically relevant reduction of the rate of exacerbations was also reported compared to S/F. Although these results cannot be considered as pivotal they supported the results of the primary outcome. The EMA concluded that the reported improvements in lung function were not large but on balance, and in comparison to the results reported for other medicinal products, could be considered as borderline clinically relevant[8].
- Since publication of the EMA assessment report, data from a subsequent clinical trial (ARGON) have been released and was included in this submission. The trial met its primary endpoint and provides further supportive evidence of comparative clinical effectiveness. IND/GLY/MF was demonstrated to be non-inferior to S/F + TIO in the 24 week study for lung function and asthma control. Improvements were seen for lung function, asthma control and moderate asthma exacerbations. However, the study was only partially blinded and had a relatively short follow-up (24 weeks) for the evaluation of exacerbations.
- Clinical expert opinion sought by AWTTC highlights this would be an option for those people already receiving high strength ICS/LABA and in need of additional bronchodilator treatment. If recommended, it would offer a single once daily treatment option for those who require a high-dose.
- Enerzair® Breezhaler® can be prescribed with or without a sensor device. The sensor delivers data on medication use to an app on the patient's smartphone. The app also sends the patient reminders to take their prescribed dose and keeps a record of medication use over time. The company suggest the sensor and app may improvement adherence[8].

4.0 COST-EFFECTIVENESS

4.1 Context

The company submission[1] includes a cost-minimisation analysis (CMA) comparing IND/GLY/MF administered once daily by inhalation with high-dose ICS/LABA twice daily plus add-on tiotropium once-daily as maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of high dose ICS/LABA and who experienced one or more asthma exacerbations in the previous year.

A Markov model with a four-week cycle length is used to estimate the difference in treatment costs between IND/GLY/MF and S/F + TIO. The model adopts a 50-year (lifetime) horizon and an NHS Wales/Personal and Social Services perspective. Patients enter the model at a mean age of 52 years, as observed in the IRIDIUM[15] and

ARGON[16] studies, with a diagnosis of inadequately controlled asthma and remain in the 'day-to-day symptoms' state until death.

Costs for a full course of treatment are calculated as the sum of the costs of medicine acquisition. Treatment acquisition costs are based on once daily IND/GLY/MF compared with twice daily S/F + once daily TIO. Medicine acquisition costs including concomitant medications were sourced from the British National Formulary[18]. Healthcare resource use costs associated with primary care or hospital visits and admissions were obtained from Personal Social Services Research Unit[19] and UK NHS reference costs[20]. Administration and monitoring costs were not included. Rescue medication costs based on mean daily puffs of salbutamol as observed in the ARGON study[16]. All costs are discounted at 3.5%.

4.2 Results

The results of the base case analysis and scenario/sensitivity analyses are detailed in Table 3. When compared with S/F + TIO, IND/GLY/MF is less costly in the base case and in all scenario/sensitivity analyses conducted. The cost differences are entirely attributed to lower medicine acquisition costs.

Table 3. Results of the base case analysis and scenario/sensitivity analyses.

Scenario	Costs	IND/GLY/MF	ICS/LABA +TIO	Difference	Plausibility
Base case					
IND/GLY/MF vs S /F + TIO	Resource use	£30,770.39	£30,770.39	£0	
	Drug costs	£10,000.61	£12,526.61	-£2,526.00	
	Rescue medication costs	£79.98	£79.98	£0	
	Total costs	£40,850.99	£43,376.98	-£2,526.00	
Scenario Analysis 1: Varying the model time horizon (10 years)					
IND/GLY/MF vs S /F + TIO	Resource use	£14,334.14	£14,334.14	£0	This scenario is less plausible than the base case as asthma is a long-term condition.
	Drug costs	£4,658.70	£5,835.42	-£1,176.72	
	Rescue medication costs	£37.26	£37.26	£0	
	Total costs	£19,030.10	£20,206.82	-£1,176.72	
Scenario Analysis 2: Varying the model time horizon (20 years)					
IND/GLY/MF vs S /F + TIO	Resource use	£23,338.50	£23,338.50	£0	This scenario is less plausible than the base case as asthma is a long-term condition.
	Drug costs	£7,585.19	£9,501.09	-£1,915.90	
	Rescue medication costs	£60.66	£60.66	£0	
	Total costs	£30,984.35	£32,900.25	£-1,915.90	
Scenario Analysis 3: Including treatment discontinuation based on ARGON					
IND/GLY/MF vs S /F + TIO	Resource use	£30,770.39	£30,770.39	£0	This scenario is plausible as it is based on observed discontinuation data.
	Drug costs	£9,757.20	£11,947.16	-£2,189.96	
	Rescue medication costs	£79.98	£79.98	£0	
	Total costs	£40,607.57	£42,797.53	-£2,189.96	

Scenario	Costs	IND/GLY/MF	ICS/LABA +TIO	Difference	Plausibility
Scenario Analysis 4: Inclusion of inpatient resource use from Wilson et al.(2014)[21]					
IND/GLY/MF vs S /F + TIO	Resource use	£32,047.04	£32,047.04	£0	This scenario is plausible using NHS reference costs and published event rates[21]. Inpatient costs in this scenario are greater than those in the base-case analysis.
	Drug costs	£10,000.61	£12,526.61	-£2,526.00	
	Rescue medication costs	£79.98	£79.98	£0	
	Total costs	£42,127.63	£44,653.63	-£2,526.00	
Scenario Analysis 5: cost of ICS/LABA + TIO based on average cost of high dose ICS/LABA combinations used in UK clinical practice					
IND/GLY/MF vs ICS/LABA + TIO	Resource use	£30,770.39	£30,770.39	£0	This scenario is plausible. It uses a weighted average cost for salmeterol/ fluticasone combinations prescribed in clinical practice based on company market share estimates.
	Drug costs	£10,000.61	£11,800.67	-£1,800.06	
	Rescue medication costs	£79.98	£79.98	£0	
	Total costs	£40,850.99	£42,651.04	£-1,800.06	
Scenario Analysis 6: cost of ICS/LABA + TIO based on average cost of Seretide® Accuhaler® and Symbicort® Turbohaler®					
IND/GLY/MF vs ICS/LABA + TIO	Resource use	£30,770.39	£30,770.39	£0	This scenario is less plausible, only considering two combinations of the comparator medication. These results are presented for consistency and comparability with a previous study[21].
	Drug costs	£10,000.61	£11,993.99	-£1,993.38	
	Rescue medication costs	£79.98	£79.98	£0	
	Total costs	£40,850.99	£42,844.37	-£1,993.38	
Societal Analysis: Inclusion of Societal Perspective (workdays lost due to asthma)					
IND/GLY/MF vs S /F + TIO	Resource use	£30,770.39	£30,770.39	£0	This scenario contradicts the notion of undertaking a CMA as it assumes differences in productivity between groups.
	Drug costs	£10,000.61	£12,526.61	-£2,526.00	
	Rescue medication costs	£79.98	£79.98	£0	
	Productivity costs	£15,185.72	£16,134.83	-£949.11	
	Total costs	£56,036.71	£59,511.81	-£3,475.11	

IND/GLY/MF: indacaterol acetate/glycopyrronium bromide/ mometasone furoate; S/F +TIO: salmeterol furoate/fluticasone plus tiotropium; ICS: inhaled corticosteroid, LABA: long acting beta agonist; CMA: cost minimisation analysis

Scenario analyses considering shorter time horizons demonstrate that a high percentage of cost savings occur in the first 20 years of treatment. Utilising alternative pricing for comparators (either average costs of high strength ICS/LABA combinations used in UK clinical practice or average cost of high strength Seretide® Accuhaler® and high strength Symbicort® Turbohaler®) result in a reduction in the incremental cost difference, yet continues to favour IND/GLY/MF in both scenarios analogous to the base-case results.

4.3 AWTTC critique

The reliability of the CMA depends on the extent to which IND/GLY/MF is considered to be therapeutically equivalent to the comparators. The company justified using a CMA, as opposed to a CUA, on the basis that the supporting study, ARGON reported non-inferior efficacy for IND/GLY/MF versus S/F + TIO. The results of the CMA indicate that IND/GLY/MF is cost-saving compared to S/F + TIO.

In the absence of well-designed equivalence trials and/or evidence of close comparability of other effects (impact on health-related quality of life, adverse events, patient preference, adherence and survival), AWTTC considers a CMA to be an inappropriate approach in this instance.

The submission is characterised by both strengths and limitations:

Strengths:

- The model reflects the relevant patient population and adopts an appropriate perspective and time horizon. The 4-week cycle-length utilised appears appropriate and consistent with other recent economic evaluations in asthma[22,23].
- The company provides a transparent and detailed account of all methods and data inputs.
- The company provides a range of sensitivity and scenario analyses to explore the impact of uncertainty on the base-case results.

Limitations:

- The company's justification for using a CMA is not convincing, given that the ARGON trial was structured to ascertain non-inferiority, which does not infer equivalence. In addition, differences were observed between treatment arms in a number of outcomes. Greater improvement on the Asthma Control Questionnaire (ACQ-7) was observed for IND/GLY/MF compared with S/F + TIO (p=0.004). Furthermore, whilst the rates of all, moderate and serve exacerbations were comparable between the two treatments, a 43% reduction in the rate of moderate exacerbations (p=0.042) was observed for IND/GLY/MF compared with S/F + TIO.
- The Markov model is likely to be an oversimplification given the available information. The model consists of two states, day-to-day symptoms and death. Furthermore, previous economic evaluations consider differences in costs associated with asthma exacerbations; the company justify the omission by assuming equal exacerbation rates between treatment arms as reported by the supporting ARGON[16] study yet differences were observed in the rate of moderate exacerbations. The omission of these cost and outcome differences are likely to bias the results by an unknown proportion. However, as ARGON[16] reports statistically significant lower rates of moderate exacerbations for IND/GLY/MF compared to SF + TIO, the omission of these cost and outcome differences are likely to bias the results in favour of SF+ TIO, with the reported incremental difference an underestimate of actual per patient costs.

- The company assumes a 0% discontinuation rate in both arms based on low rates observed in the IRIDIUM and ARGON trials. ARGON[16] reports a lower dropout rate for IND/GLY/MF (4.6%) compared to S/F + TIO (5.6%). It is unclear whether discontinuation rates would be equal in practice given the twice daily dosing frequency of S/F and the need to use a second device for the TIO delivery compared with once daily IND/GLY/MF. A scenario analysis was conducted by the company including discontinuation rates as reported in the ARGON study resulting in a small reduction in the incremental cost difference relative to the base-case results.
- The company incorporates overall age and gender-based population mortality in the model results. This is not adjusted for asthma-related mortality. Despite the ARGON[16] study observing no asthma-related or study-drug deaths, the values presented by the company are likely to overestimate life expectancy and costs for both arms.
- Adverse events were not included in the model due to the company stating that rates were low and comparable between arms. Their inclusion would add to the total costs associated with both treatments but the assumption of equal rates between arms leads to no impact on the cost difference.
- A related study[22] utilising Canadian data from the ARGON and IRIDIUM trials developed a cost-effectiveness model producing probabilistic outcomes including both costs and QALYs. The company's rationale for using a CMA is therefore difficult to justify.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) identified a conference paper detailing a CUA comparing IND/GLY/MF with S/F + TIO for patients with uncontrolled moderate-to-severe asthma from a Canadian health care payer perspective[22]. Although this source has not been peer-reviewed the results showed a difference in quality-adjusted life-years (QALYs) between the new medicine and the comparator, which suggests that a CUA may have been a more suitable approach to evaluation than a CMA in this instance.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Context and methods

The company has estimated that in Year 1 there will be 21,755 people with moderate-to-severe asthma not adequately controlled with maintenance medication increasing to 24,201 in Year 5. This estimate is based on population statistics[25] and Welsh specific prevalence data[26]. To calculate the number of people who need treatment in Wales, the company has combined incidence and prevalence estimates, including a 2.7% annual population growth rate[25] and general population mortality adjusted to the ARGON study gender proportions16. An assumed market share of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5 is applied to estimate the number of people likely to be prescribed IND/GLY/MF in Wales.

5.2 Results

The budget impact is presented in Table 4. The company estimates that introducing IND/GLY/MF would lead to an overall saving of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement

of S/F + TIO. The company carried out a sensitivity analysis using a 10% variation in the per annum market share. This changed the overall cost saving to between [commercial in confidence figure removed] and [commercial in confidence figure removed] in Year 1, increasing to between [commercial in confidence figure removed] and [commercial in confidence figure removed] in Year 5.

Table 4. Company-reported costs associated with use of IND/GLY/MF for the treatment of inadequately controlled asthma in adults.

	2021	2022	2023	2024	2025
Number of eligible patients (all licensed indications)	N/A	N/A	N/A	N/A	N/A
Sub-population of eligible patients (indication under consideration)	7,892	8,108	8,330	8,557	8,791
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without new medicine	£5,355,637	£5,502,218	£5,652,871	£5,806,916	£5,965,713
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶

The company estimates that there are no net resource implications arising from the introduction IND/GLY/MF. Cost-savings are solely attributable to reduced medicine acquisition costs.

5.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact. The company has factored population growth and mortality based on age and gender into the calculations. No asthma specific adjustment to the mortality rate has been made.
- The budget impact considerations include acquisition costs and other resource use costs such as supportive medicines costs (i.e. co-medication and rescue medication) and healthcare resource use but does not take into account costs associated with potential adverse effects based on to the assumption that these are low and comparable between treatment arms.
- The submission uses the cost of Seretide® Accuhaler® as a proxy for the cost of high strength ICS/LABA. If the company's average weighted cost for high strength ICS/LABAs is used for the comparator medicine acquisition cost the savings range from [commercial in confidence figure removed] in year 1 to [commercial in confidence figure removed] in year 5.

- The annual probability of treatment discontinuation was assumed to be 0%. This was based on low discontinuation rates within the ARGON[16] and IRIDIUM[15] trials. ARGON reports a lower dropout rate for IND/GLY/MF (4.6%) compared to S/F + TIO (5.6%). However, it is unclear whether a difference would be observed in practice given the twice daily dosing frequency of S/F and need to use a second device for TIO delivery.
- The estimates for uptake rate are based on market share assumptions made by the company and may not reflect actual rates. Sensitivity analysis for the variability of market share are presented by the company and support the base case results presented in Table 3.

GLOSSARY

ACQ-7
The Asthma Control Questionnaire ACQ-7 consists of seven questions relating to the top five scoring symptoms, FEV_1 predicted and the daily rescue bronchodilator use. The ACQ-7 score is the mean of the answers, each being scored on a scale of 0 (no impairment) to 6 (maximum impairment). A change of 0.5 points is the smallest that is considered clinically important.

AQLQ
The Asthma Quality of Life Questionnaire (AQLQ) is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma. Each question is scored on a seven-point scale (1 – totally limited/problems all the time, 7 – not at all limited/no problems). A change of score of 0.5 points is the smallest that is considered clinically important.

FEV_1
The forced expiratory volume in 1 second (FEV1) is the volume of air (in litres) exhaled in the first second during forced exhalation after maximal inspiration.

MCID
Minimal clinically important differences (MCID) are patient derived scores that reflect changes in a clinical intervention that are meaningful for the patient.

Trough FEV_1
Trough FEV_1 was defined as the average of the two FEV_1 measurements taken 23-hour 15 min and 23-hour 25 min post-evening dose. Trough FEV_1 measurements were done at Day 2, Day 184 (Week 26, the primary endpoint) and Day 365.

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