EU RISK MANAGEMENT PLAN

BUDESONIDE/ FORMOTEROL
GoResp Digihaler

RMP version to be assessed as part of this application	
RMP version number	4.1
Data lock point for this RMP	31 July 2023
Date of final sign off	22 August 2023
Rationale for submitting an updated RMP	Introduction of integrated electronics; change of product name from Budesonide/Formoterol Teva Pharma B.V. to GoResp Digihaler.
QPPV Details	
QPPV name:	Iva Novak
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy.
QPPV/deputy signature:	The signature is available on file.

Table 1: Summary of Significant Changes in This RMP Version

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part I Products overview	RMP version 3.3 (14 Jun 2021)	Introduction of integrated electronics; Change of product name from Budesonide/Formoterol Teva Pharma B.V. to GoResp Digihaler.
Part II - Module SI Epidemiology of the indications and target populations	RMP version 3.3 (14 Jun 2021)	Not applicable.
Part II - Module SII Non-clinical part of the safety specification	RMP version 3.3 (14 Jun 2021)	Not applicable.
Part II - Module SIII Clinical trial exposure	RMP version 3.3 (14 Jun 2021)	Not applicable.
Part II - Module SIV Populations not studied in clinical trials	RMP version 3.3 (14 Jun 2021)	Not applicable.
Part II - Module SV Post-authorisation experience	RMP version 3.3 (14 Jun 2021)	Module update with most recent post-authorisation exposure.
Part II - Module SVI Additional EU requirements for the safety specification	RMP version 3.3 (14 Jun 2021)	Not applicable.
Part II - Module SVII Identified and potential risks	RMP version 3.3 (14 Jun 2021)	Not applicable.
Part II - Module SVIII Summary of the safety concerns	RMP version 3.3 (14 Jun 2021)	Not applicable
Part III Pharmacovigilance plan (including post-authorisation safety studies)	RMP version 3.3 (14 Jun 2021)	Not applicable.
Part IV Plans for post-authorisation efficacy studies	RMP version 3.3 (14 Jun 2021)	Not applicable.

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	RMP version 3.3 (14 Jun 2021)	Not applicable.
Part VI Summary of the risk management plan	RMP version 3.3 (14 Jun 2021)	Change of product name from Budesonide/Formoterol Teva Pharma B.V. to GoResp Digihaler.
Part VII Annexes	RMP version 3.3 (14 Jun 2021)	Annex 8 revised to reflect changes introduced to RMP v4.1.

Other RMP versions under evaluation	
RMP Version number	Not applicable.
Submitted on	
Procedure number	

Details of the currently approved RMPs	
Version number and products covered	v3.3 BiResp® Spiromax®, DuoResp® Spiromax®, Budesonide/Formoterol Teva Pharma B.V
Approved with procedure	EMEA/H/C/002348, EMEA/H/C/003890, EMEA/H/C/004882
Date of approval (opinion date)	21 May 2021 (EMEA/H/C/002348, EMEA/H/C/003890), 14 June 2021 (EMEA/H/C/004882)

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BF	Budesonide/Formoterol
COPD	Chronic Obstructive Pulmonary Disease
e.g.	For Example
EEA	European Economic Area
EU	European Union
FEV_1	Forced Expiratory Volume in 1 Second
GINA	Global Initiative for Asthma
GVP	Good Pharmacovigilance Practices
ICS	Inhaled Corticosteroids
LABA	Long Acting Beta Agonist
PEF	Peak Expiratory Flow
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
SmPC	Summary of Product Characteristics

Part I: Product(s) Overview

Table 2: Product(s) Overview

Active substances	**Budesonide/ Formoterol**
Pharmacotherapeutic group (ATC Code)	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics (R03AK)
Marketing Authorisation Holder	Teva Pharma B.V. Swensweg 5 2031GA Haarlem The Netherlands
Medicinal products to which this RMP refers	2
Invented names in the European Economic Area (EEA)	GoResp Digihaler 160/4.5 micrograms inhalation powder GoResp Digihaler 320/9 micrograms inhalation powder
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Budesonide: Glucocorticosteroid Formoterol fumarate dihydrate: Long-acting adrenergic β_2 receptor agonists (LABA)
	Summary of mode of action: The medicinal product contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The specific properties of budesonide and formoterol allow the combination to be used either as maintenance and reliever therapy (160/4.5 µg doses), or as maintenance treatment (160/4.5 µg; 320/9.0 µg doses) of asthma. • Budesonide Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown. • Formoterol Formoterol is a selective beta$_2$-adrenoceptor agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose-dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.
	Important information about its composition:

	Not applicable.
Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.
Indications in the EEA	**Current**: Indicated in adults 18 years of age and older only. Indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β_2 adrenoceptor agonist) is appropriate: • In patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β_2 adrenoceptor agonists. or • In patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists. Symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV_1) < 70% predicted normal (post bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.
	Proposed: Not applicable.
Dosage in the EEA	**Current**: **160 micrograms / 4.5 micrograms inhalation powder** Asthma *Adults (18 years and older):* 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily. COPD *Adults (18 years and older)*: 2 inhalations twice daily **320 micrograms/9 micrograms inhalation powder** Asthma *Adults (18 years and older)*: 1 inhalation twice daily. Some patients may require up to a maximum of 2 inhalations twice daily. COPD *Adults (18 years and older)*: 1 inhalation twice daily
	Proposed: Not applicable.
Pharmaceutical forms and strengths	**Current**: [Budesonide/ Formoterol] inhalation powder, 160/4.5 µg; 320/9.0 µg delivered dose corresponding to 200/6 µg; 400/12 µg metered dose, per actuation.

	Proposed: The inhaler is white with a semi-transparent wine red mouthpiece cover and integrated electronics, for recording, storing and transmission of inhaler usage data to a mobile application (App) and a Dashboard program, upon patient/user consent.
Is the product subject to additional monitoring in the EU?	No.

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indications and Target Population

GoResp Digihaler is indicated in adults 18 years of age and older only.

Asthma

The product is indicated for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting beta$_2$-adrenoceptor agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-adrenoceptor agonists; or
- patients already adequately controlled on both inhaled corticosteroids and long-acting beta$_2$-adrenoceptor agonists.

COPD

Symptomatic treatment of patients with COPD (FEV_1 < 70% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

Epidemiology

- Asthma

Asthma is a common, life-long chronic inflammatory disease of the airways that affects children and adults of all ages. It is one of the most common chronic diseases worldwide, imposing a substantial social burden. The Global Initiative for Asthma guideline (GINA, 2020) summarises data on the prevalence, morbidity, and mortality of asthma. Asthma occurs in all countries regardless of the level of development. However, lack of a precise and universally accepted definition makes prevalence comparison problematic, but prevalence appears to range from 1% to 18% in different countries, increasing in some and stabilised in others. Reports on prevalence in Europe vary widely, between 10 to 13% in the UK, to 0.28% in Georgia. There is evidence that its prevalence has considerably increased, especially among children. Most asthma is diagnosed in childhood. Few studies report on the incidence of asthma, as it is difficult to distinguish between new and existing cases (Eagan et al, 2005).

Asthma generally requires long-term treatment. The chronic inflammation is associated with airway responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow obstruction in the lung that is often reversible, either spontaneously or with treatment. If untreated, the airway inflammation may lead to severe exacerbations requiring hospitalisation and even death, and may result in remodelling and progressively poorer lung function. When asthma is treated appropriately, these serious events are markedly reduced.

Factors that influence the risk of asthma are divided in GINA into those that cause development of disease (mainly host factors, such as genetic predisposition) and those that trigger symptoms (environmental factors, such as allergens). The mechanisms are complex and interactive; environmental factors may be important for the development of asthma in genetically susceptible individuals, and apparent ethnic differences in prevalence may reflect not only genetic differences but also differences in environmental factors, for example due to differences in socioeconomic status and lifestyle.

The prevalence of childhood asthma increased markedly in Europe in the second half of the 20th century. This is exemplified by published studies of asthma in school children in Norway, which have reported an increase in prevalence from 0.4% in 1948 to 12.3% in the mid-1990s and 20% in a study performed in 2004, although the most recent study, in 2008, reported a levelling off to 17.6%. The increase was initially most marked in Western Europe. The questionnaires developed for the International Study of Asthma and Allergy in Childhood (ISAAC) have provided a common tool for assessing the prevalence of asthma and wheezing disorders in children. In the ISAAC study performed in 1997, the highest prevalence of childhood asthma in Europe was found in the British Isles, with the prevalence of 'asthma ever' (lifetime prevalence of asthma) ranging from 1.6% in Albania to 20.7% in the UK for 13–14-year-old children, and from 1.4% in Estonia to 22.9% in the UK among 6–7-year-olds. This East-to-West difference has diminished over recent years with a relative increase in lifetime prevalence in Eastern Europe compared with the West; this may be related to simultaneous changes in lifestyle in Eastern Europe (European lung white book, 2020).

The development and persistence of asthma are driven by gene-environment interactions. Though age at onset for asthma can be at any time, most asthmatics are diagnosed in childhood. Prior to the age of 14, the prevalence of asthma is nearly twice as great in boys as in girls. For adults, asthma can begin in response to sensitizing agents through indoor or outdoor environmental exposures. An estimated 5-20% of new cases of adult-onset asthma can be attributed to occupational exposure (GINA, 2020).

- COPD

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow obstruction that is only partly reversible, inflammation in the airways, and systemic effects or comorbidities. The main cause is smoking tobacco, but other factors have been identified. Several pathobiological processes interact on a complex background of genetic determinants, lung growth, and environmental stimuli. The disease is further aggravated by exacerbations, particularly in patients with severe disease, up to 78% of which are due to bacterial infections, viral infections, or both (Decramer et al, 2012).

In 1990, the total deaths from COPD were estimated at 2.2 million and it was ranked the sixth leading cause of death. Even by conservative estimates, it is thought that the worldwide number of deaths in 2020 will be 3.5 million and COPD will be ranked third amongst the leading causes of death. During 2000, an estimated 10 million US adults reported physician-diagnosed COPD and in the USA alone, COPD was responsible for 8 million office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalisations, and 119,000 deaths. The greatest risk factor for disease development in the developed world is tobacco smoke; however, in the developing world biomass fuels have been implicated particularly in women.

Worldwide, COPD affects 9.8% of men and 5.6% of women. The prevalence rates of COPD appear to have peaked in UK men but are continuing to rise in women. This reverse in the gender trend in COPD prevalence in the developed world has been confirmed by reports from Austria that have found equal prevalence in both genders for COPD as well as tobacco use. Thus, the prevalence of COPD in women can be expected to rise worldwide over the next decade.

The annual rate of COPD exacerbations has been estimated from several different studies to be as low as 0.5 to a high of 3.5 exacerbations per patient. Hospitalisation rates have depended on type of study but range from as low as 0.09 to 2.4 per patient per year (Seemungal et al, 2011).

Treatment options/Concomitant medications in the target population

- Asthma

The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side effects of treatment. Beta-agonists are potent bronchodilators used to relieve acute symptoms, while corticosteroids (inhaled and systemic) are usually effective in reducing the airway inflammation associated with persistent asthma (see Table 3 for the current GINA recommendations).

Other medications such as leukotriene inhibitors and long acting bronchodilators are frequently added to the therapeutic regimen to attempt to optimise control of asthma symptoms. Other medications include short-acting β_2 agonists[1], anticholinergics, short-acting theophylline, and epinephrine/adrenalin injection as relievers (GINA, 2020).

About 10% of patients with severe asthma remain poorly controlled despite optimal treatment and these patients have the greatest morbidity and mortality (Banh, 2011).

- COPD

Bronchodilators constitute the mainstay of COPD treatment; β_2 agonists and long-acting anticholinergic agents are frequently used (the former often with inhaled corticosteroids). Besides improving symptoms, these treatments are also thought to lead to some degree of disease modification (Decramer et al, 2012).

Inhaled corticosteroids have similar effects on quality of life but inhalation corticosteroids/long-acting bronchodilator combinations and the long-acting antimuscarinic tiotropium all improve health status and exacerbation rates and are likely to have an effect on mortality but perhaps only with prolonged use. Erythromycin has been shown to decrease the rate of COPD exacerbations (Seemungal et al, 2011).

[1] Note: For safety, GINA no longer recommends treatment in adults and adolescents with short-acting β_2 agonist alone.

Table 3: Current Treatment Paradigm According to Global Initiative for Asthma (simplified according to GINA, 2020)

Treatment	Step 1	Step 2	Step 3	Step 4	Step 5
	Asthma education Environmental control				
Preferred controller choice	As-needed low dose ICS-formoterol	Daily low dose ICS, or as-needed low dose ICS-formoterol	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	Low dose ICS taken whenever SABA is taken	Daily LTRA or low dose ICS taken whenever SABA taken	Medium dose ICS, or low dose ICS + LTRA	High dose ICS, add-on tiotropium, or add-on LTRA	Add low dose OCS, but consider side-effects
Reliever	As-needed low dose ICS-formoterol		As-needed low dose ICS/formoterol for patients prescribed maintenance and reliever therapy		
Other reliever option	As-needed SABA				

Anti-IgE = anti-immunoglobulin E therapy; ICS = inhaled corticosteroids, LABA = long acting β_2-agonists; LTRA = leukotriene receptor antagonists; OCS = oral corticosteroids; SABA = Short acting beta agonist
Source: Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2020.

Co-morbidities found in the target population

- Asthma

Asthma is often associated with various comorbidities. The most frequently reported asthma comorbid conditions include rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnoea, hormonal disorders, and psychopathologies. These conditions may share a common pathophysiological mechanism with asthma and may influence asthma control, its phenotype and response to treatment (Boulet & Boulay, 2011).

Asthma is also associated with the atopic march, which is generally characterised by the progression of atopic dermatitis to asthma and allergic rhinitis during the first several years of life (Spergel, 2010). In addition, chronic use of corticosteroids may be associated with clinically significant complications including local effects such as dysphonia and oral candidiasis and potentially serious systemic effects associated with cortisol suppression including growth retardation, glucose intolerance and increased risk for osteoporosis and fractures (Corren, 2013).

Allergic rhinitis is ubiquitous in patients with allergic asthma, and is an important characteristic of the allergic asthma phenotype. It is considered that more than 80% of patients with asthma have rhinitis (Boulet and Boulay, 2011, Corren, 2013). As much as 75% of asthmatic patients also have chronic symptoms of rhinosinusitis, irrespective of asthma severity (Bresciani et al, 2001), although evidence of sinusitis, as assessed by sinus computed tomography, may be present in up to 84% of severe asthmatic patients (ten Brinke et al, 2002).

- COPD

Comorbidities of COPD include ischaemic heart disease, diabetes, and lung cancer (Decramer et al, 2012).

Comorbidities, such as atherosclerotic disease, depression, chronic kidney disease, cognitive impairment, obstructive sleep apnoea syndrome, lung cancer, osteoporosis, diabetes, heart failure, sarcopoenia, aortic aneurysm, arrhythmias, and pulmonary embolism are highly prevalent among older COPD patients (Corsonello et al, 2011).

Part II: Module SII - Non-Clinical Part of the Safety Specification

Not applicable. This application concerns hybrid medicinal combinations of products that have been in clinical use for over a decade. As far as the applicant is aware, the clinical safety profile is well established. No significant risk for human safety is expected with therapeutic doses of BF inhalation powder 160/4.5 µg; 320/9.0 µg delivered dose corresponding to 200/6 µg; 400/12 µg metered dose, per actuation, based on non-clinical safety data.

Part II: Module SIII - Clinical Trial Exposure

Note: The clinical trial data was taken from the Developmental Safety Update Report (DSUR) prepared for Budesonide/Formoterol Spiromax® Inhalation Powder with cut-off date on 31 October 2018.

During the development program, approximately 1,414 subjects and patients have received at least one dose of Budesonide/Formoterol (BF) Spiromax®.

Estimates of overall cumulative subject exposure to BF Spiromax® based upon exposure data from completed studies are provided in Table 4.

Table 4: Estimated Overall Cumulative Exposure in Completed Studies with BF Spiromax

Study number	Number of subjects/patients	
	BF SPIROMAX	SYMBICORT TURBUHALER
AS-101	18	18
BFC-AS-102	18	18
BFS-AS-103	88	88
BFS-AS-104	90	90
BFS-AS-105	88	88
BFS-AS-106	56	56
BFS-AS-107	72	72
BFS-BE-108	88	88
BFS-BE-109	90	90

Study number	Number of subjects/patients	
	BF SPIROMAX	SYMBICORT TURBUHALER
BFS-BE-110	20	20
BFS-BE-112	90	90
BFS-AS-305	74	75
BFS-AS-306	303	299
BFS-AS-40035[1]	197	197
BFS-AS-307	122[2]	123
Estimated total	**1,414**	**1,412**

[1] One patient was eligible for Stage 2; however, no device was available at the time and the patient withdrew before treatment was allocated.

[2] A total of 123 patients in the BF SPIROMAX® group were randomized, but one patient was not dosed.

The cumulative numbers of subjects/patients receiving BF Spiromax® in the completed studies by age group, sex, and racial group are provided in Table 5 and Table 6.

Table 5: Estimated Cumulative Exposure to BF Spiromax in Completed Studies by Age Group, Sex, and Racial Group

Estimated Cumulative Exposure to BF SPIROMAX in Completed Studies by Age Group, Sex, and Racial Group								
Study protocol	**BFC-AS-101 (N=18)**	**BFC-AS-102 (N=18)**	**BFS-AS-103 (N=88)**	**BFS-AS-104 (N=90)**	**BFS-AS-105 (N=88)**	**BFS-AS-106 (N=56)**	**BFS-AS-107 (N=72)**	**BFS-BE-108 (N=88)**
Age group, years								
Mean (SD)	27.2 (6.8)	25.3 (4.1)	31.7 (7.7)	29.7 (5.1)	27.8 (7.1)	28.7 (6.7)	29.2 (6.1)	27.7 (7.3)
Min	18	19	18	19	18	21	20	18
Max	42	36	45	44	45	45	45	45
Sex (%)								
Men	10 (55.6)	11 (61.1)	46 (52.3)	56 (56.22)	65 (73.9)	18 (32.14)	56 (77.8)	51 (58.0)
Women	8 (44.4)	7 (38.9)	42 (47.7)	34 (37.78)	23 (26.1)	38 (67.9)	16 (22.2)	37 (42.0)
Race (%)								
White	18 (100)	17 (94.4)	85 (96.6)	60 (66.7)	71 (80.7)	36 (64.3)	53 (73.6)	43 (48.9)
Black	—	1 (5.6)	—	—	7 (8.0)	—	—	37 (42.0)
Asian	—	—	2 (2.3)	8 (8.9)	6 (6.8)	8 (14.3)	13 (18.1)	1 (1.1)
American Indian or Alaskan Native	—	—	—	—	—	—	—	—
Pacific Islander	—	—	—	—	—	—	—	—
African	—	—	—	16 (17.8)	—	12 (21.4)	4 (5.6)	—
Others	—	—	1 (1.1)	6 (6.7)	4 (4.5)	—	2 (2.8)	7 (8.0)

Table 6: Estimated Cumulative Exposure to BF Spiromax in Completed Studies by Age Group, Sex, and Racial Group (Continued)

Estimated Cumulative Exposure to BF SPIROMAX in Completed Studies by Age Group, Sex, and Racial Group								
Study protocol	**BFS-BE-109 (N=90)**	**BFS-BE-110 (N=20)**	**BFS-BE-112 (N=90)**	**BFS-AS-305 (N=77)[1]**	**BFS-AS-306 (N=303)**	**BFS-AS-40035 (N=197)**	**BFS-AS-307 (N=123)2**	**Estimated total**
Age group, years								
Mean (SD)	29.4 (6.6)	30.6 (8.6)	31.7 (8.1)	8.6 (1.5)	48.1 (16.2)	53.3 (14.3)	46.1 (13.3)	NA
Min	19	20	18	6	12	18	21	NA
Max	45	45	45	11	83	74	75	NA
Sex (%)								
Men	48 (53.3)	10 (50)	54 (60.0)	46 (59.7)	131 (43)	81 (41.1)	56 (46)	739
Women	42 (46.7)	10 (50)	36 (40.0)	31 (40.3)	172 (57)	116 (58.9)	67 (54)	679
Race (%)								
White	43 (47.8)	11 (55)	83 (92.2)	77 (100)	297 (98)	189 (95.9)	—	1083
Black	35 (38.9)	8 (40)	2 (2.2)	—	2 (<1)	3 (1.5)	—	95
Asian	2 (2.2)	1 (5)	2 (2.2)	—	1 (<1)	3 (1.5)	123 (100)	170
American Indian or Alaskan Native	—	—	—	—	—	—	—	—
Pacific Islander	1 (1.1)	—	—	—	—	—	—	1
African	—	—	—	—	—	—	—	32
Others	9 (10.0)	—	3 (3.3)	—	3 (<1)	2 (1)	—	37

[1] The demographic data presented is based on Safety population and therefore the total number of subjects may not align with table above.

[2] A total of 123 patients in the BF SPIROMAX group were randomized, but one patient was not dosed. The demographic data presented is based on ITT population and therefore the total number of subjects may not align with table above.

*BF=budesonide formoterol fumarate dihydrate; ITT=intent-to-treat min=minimum; max=maximum; N= number of subjects

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

For presentation of special populations included or not in clinical trial development programme, refer to Table 7.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Not Represented in Clinical Trial Development Programmes

Table 7: Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Comment
Children	**Children 6-11 years of age** Teva conducted Study BFS-AS-305 in subjects aged 6-11 years with asthma. It was conducted to assess the systemic effects of ICS in children with asthma using two, sensitive measures - measuring linear growth rate (by knemometry) and investigating hypothalamic-pituitary function (by measuring 24-hour cortisol excretion). The AE profile in Study BFS-AS-305 confirmed a similar safety profile for BF Spiromax 80/4.5 mcg and Symbicort® Turbuhaler® 100/6 mcg, with 8 (10.8%) subjects experiencing at least one AE on BF 80/4.5 mcg compared with 6 subjects (8.0%) on Symbicort® Turbuhaler® 100/6 mcg and 11 subjects (14.7%) on placebo. **Adolescents >12 years of age** Teva also conducted Study BFS-AS-306 in subjects 12 years of age or older with persistent asthma to establish the non-inferiority of the BF 160/4.5 μg relative to Symbicort® Turbuhaler® 200/6 μg. BF 160/4.5 μg was non-inferior to the Symbicort® Turbohaler® 200/6 μg with respect to primary endpoint: change from baseline in weekly average of daily through morning PEF. The safety profile of BF was comparable to the established profile of Symbicort® Turbohaler® with no new safety signals observed. There was no statistically significant difference in change of device preference from baseline to week 12. The safety profile of BF was similar to that of Symbicort® Turbohaler®. **Overall Safety in Children and Adolescents** The reference product Symbicort® Turbuhaler® is approved for treatment of asthma as a maintenance therapy in children 6 years and older. Only limited data are available for use of fixed combination of budesonide/ formoterol in children under 6 years. It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In

Type of special population	Comment
	addition, consideration should be given to referring the patient to a paediatric respiratory specialist. Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment. Long-term studies with inhaled budesonide in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of budesonide/ formoterol at higher doses is available. Interaction studies have only been performed in adults. The pharmacokinetics of formoterol in children have not been studied.
Pregnant women	For BF or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-foetal development study in the rat showed no evidence of any additional effect from the combination. There are no adequate data from use of formoterol in pregnant women. In animal studies, formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels. Data on approximately 2,000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies, glucocorticosteroids have been shown to induce malformations. This is not likely to be relevant for humans given recommended doses. Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease, and permanent changes in glucocorticoid receptor density, neurotransmitter turnover, and behaviour at exposures below the teratogenic dose range. During pregnancy, BF should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.
Breastfeeding women	Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of BF to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.
Patients with hepatic impairment	There are no data available for use of BF in patients with hepatic impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.
Patients with renal impairment	There are no data available for use of BF in patients with renal impairment. The pharmacokinetics of budesonide or formoterol in patients with renal failure are unknown.
Patients with relevant comorbidities	BF is contraindicated in patients with hypersensitivity (allergy) to budesonide or formoterol. BF is contraindicated in patients with hypersensitivity (allergy) to lactose (which contains small amounts of milk protein). BF contains lactose monohydrate. This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

Type of special population	Comment
	Patients should not be initiated on BF during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to BF therapy. BF should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm, or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias, or severe heart failure. Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval. The need for, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances.

Part II: Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

Note: data was taken from the Periodic Safety Update Report with cut-off date on 24 August 2022.

SV.1.1 Method Used to Calculate Exposure

Estimation of cumulative exposure from post marketing sources was calculated based on data collected from Teva and acquired companies. An estimate of patients exposed to BF fixed-dose combination was calculated based on the World Health Organization (WHO) recommended Defined Daily Dose (DDD) for budesonide of 800 μg.[2]

SV.1.2 Exposure

Table 8: Exposure Table by Region, Formulation and Strength

EEA/NON EEA	Formulation	Strength	Sum of Number of DDDs	Sum of Estimation of patients-years
EEA	Inhalation Powder	160/4.5 mcg/dose	251.171.628	688.141
EEA		320/9 mcg/dose	190.572.840	522.117

[2] WHO Collaborating Centre for Drug Statistics Methodology, ATC/DDD Index, 2019. Available at: http://www.whocc.no/atc_ddd_index/

EEA/NON EEA	Formulation	Strength	Sum of Number of DDDs	Sum of Estimation of patients-years
EEA total			441.744.468	1.210.259
NON EEA	Inhalation powder	160/4.5 mcg/dose	153.569.232	420.738
NON EEA		320/9 mcg/dose	84.616.320	231.826
Non EEA total			238.185.552	652.563
Total			679.930.020	1.862.822

Cumulatively, until 24 August 2022, it is estimated that approximately 679,930,020DDDs of Teva Group BF were sold. Cumulative estimated exposure to Teva Group products containing BF fumarate was approximately 1,862,822 patient-years.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The MAH considers the potential for misuse for illegal purposes as unlikely.

Part II: Module SVII - Identified and Potential Risks

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 9: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

There are no safety concerns recognised for GoResp Digihaler, in line with the reference product Symbicort® Turbuhaler®.

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

Additional pharmacovigilance requirements are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

III.1 Routine Pharmacovigilance Activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are proposed.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable. No post-authorisation efficacy studies with Budesonide/ Formoterol have been planned.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3. Summary of Risk Minimisation Measures

Not applicable.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for GoResp Digihaler

This is a summary of the risk management plan (RMP) for GoResp Digihaler. The RMP details important risks of GoResp Digihaler, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information).

GoResp Digihaler summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how GoResp Digihaler should be used.

This summary of the RMP should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary as part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of GoResp Digihaler RMP.

I. The Medicine and What It is used for

The product is indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β_2-adrenoceptor agonist) is appropriate, as well as for the symptomatic treatment of patients with severe COPD and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators (see SmPC for the full indication). It contains fixed-dose combination of active substances budesonide and formoterol and it is given as inhalation powder.

Further information about the evaluation of GoResp Digihaler benefits can be found in EPAR, including in its plain-language summary, available on the EMA website.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of GoResp Digihaler, together with measures to minimise such risks and the proposed studies for learning more about GoResp Digihaler risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of GoResp Digihaler are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of GoResp Digihaler. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 10: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

II.B Summary of Important Risks

The safety information in the proposed product information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of GoResp Digihaler.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for GoResp Digihaler.

Part VII: Annexes

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Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6 – Details of Proposed Additional Risk Minimisation Activities

Not applicable.