MODULE 2.5

CLINICAL OVERVIEW

NAME OF PRODUCT: **BECLOMETASONE DIPROPIONATE PRESSURISED INHALATION SOLUTION**

ACTIVE SUBSTANCES: **BECLOMETASONE DIPROPIONATE**

FORMULATION: **PRESSURISED INHALATION SOLUTION**

DATE OF REPORT: **DECEMBER 2020**

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LIST OF ABBREVIATIONS

Abbreviation	Full form
ALT	Alanine aminotransaminase
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartame aminotransaminase
BMD	Bone mineral density
C-ACT	Childhood asthma control test
CFCs	Chloroflurocarbons
CSC	Central serous chorioretinopathy
DALYS	Disability adjusted life years
FEF_{25}	Forced expiratory flow at 25% FVC
FEV_1	Forced expiratory volume in 1s
FVC	Forced Vital capacity
GI	Gastrointestinal
HFA-134A	Hydrofluoroalkane
HPA	Hypothalamo-pituitary-adrenal axis
ICS	Inhaled corticosteroids
ITT	Intention-to-treat
MDI	Metered dose inhalers
MEF_{50}	Mid expiratory flow at 50 % of the forced vital capacity
PC_{20}	Provocative concentration
PD	Pharmacodynamics
PD_{20}	Provocative dose
PEFR	Peak expiratory flow rate
PK	Pharmcokinetics
SDS	Standard deviation scores
TA	Triamcinolone acetonide
VAS	Visual Analog Scale
WHO	World Health Organisation
WPF	Wright Peak Flow

2.5.1 PRODUCT DEVELOPMENT RATIONALE

The Applicant has developed beclometasone dipropionate pressurised inhalation solution 100 µg and 200 µg. This application is being submitted under Article 10(3) (hybrid application) of European Directive 2001/83/EC (as amended) based on *in vitro* BE studies conducted with Clenil Modulite inhaler (marketed by Chiesi Limited, UK) as reference product and published scientific bibliographical evidences supporting the risk benefit profile for beclometasone dipropionate (BDP).

Beclometasone dipropionate was the first effective and safe inhaled corticosteroid (ICS) to be marketed. It was first available in 1972, commonly delivered via pressurized aerosols [metered dose inhalers (MDIs)], for the prophylactic management of mild, moderate, or severe asthma in adults or children. Hydrofluoroalkane (HFA-134a) has been developed as a replacement propellant for use in MDIs since it is chemically inert, non-flammable and of low toxicity. In 1994, the European committee for proprietary medicinal products (CPMP) concluded that HFA-134a could be a suitable alternative to chloroflurocarbons (CFCs) used in the formulation of medicinal products, including pressurized MDIs, for treatment of asthma.

Asthma is a chronic disease of the air passages of the lungs which inflames and narrows them. It was estimated that more than 339 million people had asthma globally in 2016 which is a common disease among children. According to World Health Organisation (WHO) estimates, there were 417,918 deaths due to asthma at the global level and 24.8 million disability adjusted life years (DALYS) attributable to asthma in 2016. The most recent guidelines from the U.S. national asthma education and prevention program promote the early use of ICs for all asthma patients, except those with mild intermittent disease, in order to prevent lung damage. Similarly, updated British asthma guidelines advocate aggressive use of ICs. For example, in contrast to the former approach of gradually increasing the dosage of ICs until symptoms are controlled, it is recommended that early treatment be initiated with higher dosages and then tapered to the lowest effective dosage (Webb DR et al, 1998).

Beclometasone dipropionate (BDP) is actually a pro-drug with weak glucocorticoid receptor binding affinity, that is hydrolysed via esterase enzymes to an active metabolite beclometasone 17-monopropionate (B-17-MP). In asthmatic patients, the inhaled drug has little immunosuppressive effect and causes minimal changes in circulating leucocytes and eosinophils. Although antigen-induced type I immediate asthmatic and nasal reactions are not inhibited by prechallenge administration of single doses of BDP, regular treatment for 1 week prior to antigen challenge inhibits such reactions in some patients. Substitution of inhaled BDP for oral maintenance corticosteroids in patients with asthma generally results in an improvement in adrenal function when the oral steroids have been administered daily.

Inhaled BDP is well established in the management of asthma. Studies conducted over the last decade have confirmed that inhaled beclometasone dipropionate 400 to 800 µg daily can reduce the need for oral maintenance corticosteroids in the majority of asthmatic patients requiring such therapy, and that increasing the dosage to 2000 µg daily may provide additional clinical

benefit in some patients unresponsive to usual therapeutic dosages. Follow-up over a period of several years has confirmed that the initial response to inhaled beclometasone can be maintained in most patients.

The overview is prepared to support the information claimed in the proposed Summary of Product Characteristics of beclometasone dipropionate 100 µg and 200 µg. Published literature available for beclometasone dipropionate is discussed in subsequent sections of this report.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

The *Guideline on the requirements for clinical documentation for Orally Inhaled Products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for use in the treatment of Asthma in Children and Adolescents (2009)* (CPMP/EWP/4151/00 Rev. 1), describes the requirements for abridged applications to demonstrate therapeutic equivalence to a reference medicinal product. The guideline states that the *"use of only comparative in vitro data, obtained with an accepted method (e.g. multistage impactor/impinger), may be considered acceptable if the product satisfies all of the [following] criteria (compared with the reference product)"* (reference made to criteria listed in the Guideline).

The proposed product satisfies all the required criteria, and therefore Lupin proposes to use an i*n vitro* only assessment to demonstrate therapeutic equivalence between the proposed product and the Reference prduct. Consequently this submission is not supported by a clinical study.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 Pharmacokinetics

Absorption

A study assessed the absolute bioavailability and pharmacokinetics (PK) of BDP in man following intravenous (IV), oral, intranasal and inhaled administration in 12 healthy subjects. It was administered via the following routes: IV infusion (1000 µg), oral (4000 µg, aqueous suspension), intranasal (1344 µg, aqueous nasal spray) and inhaled (1000 µg ex-valve, MDI). BDP was not detected in plasma following oral or intranasal dosing. The mean absolute bioavailability of inhaled BDP was 2% (1–4%) and not reduced by coadministration of charcoal. The mean percentage *F* of the active metabolite B-17-MP was 62% (47–82%) for inhaled dosing without charcoal, respectively. The corresponding estimates of nasal and lung absorption, based on the coadministration of charcoal, were < 1% and 36% (27–47%), respectively. Unchanged drug has negligible oral and intranasal bioavailability with limited absorption following inhaled dosing due to extensive (95%) presystemic conversion of BDP to B-17-MP in the lung. The oral and intranasal bioavailabilities of the active metabolite B-17-MP were high and similar, but direct absorption in the nose was insignificant. The total inhaled bioavailability of B-17-MP (lung + oral) was also high (62%) and approximately 36% of this was due to pulmonary absorption. Estimates of oral bioavailability and pulmonary deposition based on total beclometasone (BOH) were approximately half of those found for B-17-MP (Daley-yates et al, 2001).

Table 1: Pharmacokinetic parameters for BDP and B-17-MP following administration of BDP via the inhaled route with and without activated charcoal

Group	Analyte	AUC (pg ml^{-1} h)	C_{max} (pg ml^{-1})	t_{max} (h)	$t_{1/2}$ (h)	MRT (h)	MAT (h)
Inhaled	BDP	151	319	0.3*	–	–	–
		(84.6–269)	(184–553)	(0.2–0.5)			
	B-17-MP	3851	944	1.0*	2.7*	4.1	0.6
		(2831–5238)	(671–1327)	(0.8–6.0)	(2.1–3.6)	(3.5–4.6)	(−2.1–1.8)
Inhaled	BDP	217#	459	0.5*	–	–	–
with charcoal		(134–353)	(294–716)	(0.2–0.5)			
	B-17-MP	2383	705	0.8*	2.3*	3.5	−0.2
		(1541–3686)	(436–1141)	(0.8–1.0)	(1.7–5.8)	(3.0–4.0)	(−2.2–2.3)

Values are geometric mean (95% CI) except values denoted with* which are median (range) #Denotes AUC (0, *t*).

Table 2: Relative systemic exposure and absolute bioavailability of BDP, B-17-MP and calculated total BOH following administration of BDP intravenously and via the oral, intranasal and inhaled routes with and without activated charcoal

		AUC normalized to a 1000 µg dose		Bioavailability relative to intravenous[2]			
Route	**Analyte[1]**	**No charcoal AUC (pg ml^{-1} h)**	**With charcoal AUC (pg ml^{-1} h)**	**Total (%F)**	**Oral (%F)**	**Lung (%F)**	**Nose (%F)**
Intravenous	BDP	6660	–	100	–	–	–
Inhaled	BDP	151	217	2	0	2	–
Intravenous	B-17-MP	6185	–	100	–	–	–
Oral	B-17-MP	2540	58	41	41	–	–
Intranasal	B-17-MP	2723	67	44	43	–	< 1
Inhaled	B-17-MP	3851	2383	62	26	36	–
Intravenous	Total BOH	10138	–	100	–	–	–
Oral	Total BOH	2132	49	21	21	–	–
Intranasal	Total BOH	2287	56	23	22		< 1
Inhaled	Total BOH	3343	2158	33	13	20	

[1]Total BOH is the sum of the measured BDP, B-17-MP and BOH AUC values expressed as BOH equivalents.
[2]Values corrected for charcoal block efficiency.

An open-label, randomized, single-dose, 2-period crossover study was conducted to determine the beclometasone (BOH) availability of oral BDP relative to inhaled HFA BDP in 40 mild asthmatic patients. Each patient received an oral dose of BDP (0.2, 0.5, 1, 2 or 5 mg) in 1 period and an inhaled dose of BDP (0.2 or 0.8 mg) in the other period, with 4 patients allocated to each of 10 different treatment sequences. The BOH availability of orally administered BDP was approximately 40% relative to inhaled HFA BDP. In addition, the fraction of an oral dose that reaches the systemic circulation was estimated from the 40% relative availability and previous lung deposition data to be 0.26 (Soria I et al,1998).

A double-blind study examined the PK after 14 days of dosing with HFA-BDP. A total of 43 steroid-naive asthmatic patients were randomised into 5 parallel groups and dosed every 12 h for 14 days with: HFA-placebo; 200, 400 or 800 µg/day HFA-BDP; or 800 µg/day CFC-BDP. The highest concentrations of total beclometasone were seen at the first blood sampling time (1 h) in almost all patients in the active treatment groups. The derived PK parameters showed that the rate and extent of total-beclometasone absorption increased with increasing doses of HFA-BDP ($P<0.0001$). The extent of drug absorption (steady-state AUC values) from 800 µg/day HFA-BDP and CFC-BDP was in the ratio of 1:7:1 (Harrrison LI et al, 1999).

A study measured serum levels and dose proportionality of the beclometasone derived from BDP. A total of 13 mild-moderate asthmatic patients received a single dose of 8 inhalations from each strength according to a double-blind crossover design. For the total doses of 400, 800, and 1600 µg studied over 12 h, C_{max} and AUC increased in a ratio of 1:1·8:3·1. A good correlation was seen between the fine-particle mass delivered and the *in vivo* performance of the 3 strengths. From a clinical point of view, the predictable increases in serum levels with an increase in dose will permit the clinician to effectively titrate a patient with this product (Harrison LI et al, 1997).

A study compared the serum PK of the metabolites of BDP after inhalation from CFC and HFA formulations in asthmatic patients in 23 patients. Each patient received in separate periods 200 µg or 400 µg HFA-BDP, or 400 µg CFC-BDP. Following a 400 µg BDP dose, the HFA formulation gave mean C_{max} and AUC values of beclometasone esters of 1153 pg/mL and 4328 pg h/mL, respectively, and beclometasone C_{max} and AUC values of 69 pg/mL and 682 pg h/mL, respectively. These values were approximately 2-3-fold in those seen with the CFC formulation (beclometasone esters C_{max} and AUC of 380 pg/mL and 1764 pg h/mL, respectively; beclometasone C_{max} and AUC of 41 pg/ml and 366 pg h/mL, respectively). Beclometasone esters peaked significantly earlier for the HFA formulation (0.8 h) than for the CFC formulation (2 h). The more rapid and greater efficiency of systemic drug delivery of the HFA formulation compared with the CFC formulation can be explained if most of each inhalation from CFC-BDP is swallowed and absorbed orally, whereas most of each inhalation from HFA-BDP is absorbed through the lungs (Harrison LI et al, 1999).

Systemic absorption of unchanged BDP occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged BDP. Prior to absorption there is extensive conversion of BDP to its active metabolite B-17-MP. The systemic absorption of B-17-MP arises from both lung deposition (36%) and oral absorption of the swallowed dose (26%). The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged BDP and B-17-MP, respectively. BDP is absorbed rapidly with peak plasma concentrations observed (t_{max}) at 0.3 hours. B-17-MP appears more slowly with a t_{max} of 1 hour. There is an approximately linear increase in systemic exposure with increasing inhaled dose. When administered orally the bioavailability of BDP is negligible but pre-systemic conversion to B-17-MP results in 41% of the dose being absorbed as B-17-MP (SmPC of Clenil Modulite, Chiesi Ltd, December 2018).

Distribution

A study assessed the PK of BDP in man following IV, oral, intranasal and inhaled administration in 12 healthy subjects. BDP was not extensively distributed to the tissues (V_{ss}, 20 l) but was eliminated rapidly with a high clearance (150 l/h) and short half-life (0.5 h). In comparison with BDP, the tissue distribution of B-17-MP was extensive (V_{ss}, 424 l). Since both BDP and B-17-MP are lipophilic molecules, a large V_{ss} was expected. Although this was found for B-17-MP, the value for BDP was considerably smaller. The plasma protein binding (87%) is not high enough to limit tissue distribution of BDP, but one factor that may have

influenced V_{ss} is rapid metabolism in the blood and well perfused tissues, resulting in the near complete elimination of BDP before maximal tissue distribution is achieved. Therefore, the apparent V_{ss} for BDP is dominated by the initial rapid elimination phase, leading to smaller value than expected (Daley-yates et al, 2001).

The tissue distribution at steady-state for BDP is moderate (20 L) but more extensive for B-17-MP (424 L). Plasma protein binding is moderately high (87%) (SmPC of Clenil Modulite, Chiesi Ltd, December 2018).

Metabolism

BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite B-17-MP. Minor inactive metabolites, B-21-MP and BOH are also formed but these contribute little to the systemic exposure (SmPC of Clenil Modulite inhaler, Chiesi Ltd, December 2018). A study assessed the metabolism of BDP in man following IV, oral, intranasal and inhaled administration in 12 healthy subjects. The high clearances of BDP and B-17-MP indicate extensive extra-hepatic metabolism, which is in agreement with their wide tissue distribution, the major route of elimination being mediated by high capacity esterases. It is also apparent that B-17-MP clearance is elimination rate limited whereas BOH demonstrated formation rate limited kinetics (Daley-yates et al, 2001).

Excretion

A study assessed the PK of BDP in man following IV, oral, intranasal and inhaled administration in 12 healthy subjects. BDP was eliminated rapidly with a high clearance (150 L/h) and short half-life (0.5 h). The disappearance of BDP was accompanied by the appearance of B-17-MP and after a delay of approximately 1.5 h transient BOH concentrations were detected in plasma. Based on the mean concentration-time data, the elimination half-life of BOH appeared to be similar to that of B-17-MP. The most significant component in plasma was B-17-MP. Its elimination half-life (2.7 h) was longer than that found for BDP but its clearance (120 L/h) was similar (Daley-yates et al, 2001).

The elimination of BDP and B-17-MP are characterised by high plasma clearance (150 L/h and 120 L/h) with corresponding terminal elimination half-lives of 0.5 hours and 2.7 hours. Following oral administration of tritiated BDP, approximately 60% of the dose was excreted in the faeces within 96 hours mainly as free and conjugated polar metabolites. Approximately 12% of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of BDP and its metabolites is negligible (SmPC of Clenil Modulite, Chiesi Ltd, December 2018).

Special Populations

Pediatrics

A study evaluated lung deposition, systemic availability, and basic PK parameters of BDP in children with chronic asthma. Plasma levels of BDP (17-BMP and 21-BMP), and beclometasone were measured after an IV infusion of 60 µg BDP and after inhalation of A) 100 µg HFA-BDP, B) 200 µg HFA-BDP, C) 200 µg HFA-BDP after ingestion of charcoal to block gastrointestinal (GI) absorption of drug, and D) 400 µg CFC-BDP. Treatments A-D was given in a randomized, cross-over design. 14 patients aged 10-14 years completed all 5 study days. The mean systemic bioavailabilities in percent of dose leaving the canister valve (ex-valve) were 70% (100 HFA), 74% (200 HFA), 60% (200 HFA + charcoal), and 27% (400 CFC). After HFA treatment, 82% of the systemically available dose was absorbed through the lungs and 18% from the GI tract. The estimated bioavailability of BDP from the GI tract was 68%. BDP was metabolized to 17-BMP within minutes. Mean steady-state volume of distribution of 17-BMP was 84 L, and the mean terminal $t_{1/2}$ after the 4 inhalations was 2.7 h (range, 2.2-3.7 h). Mean $t_{1/2}$ and clearance after IV administration were 1.7 h and 0.9 L/min, respectively (Agertoft L et al, 2003).

Pharmacokinetic Interactions

An open label, prospective, randomized study assessed the safety and PK of BDP and its active metabolite, 17-BMP, in combination with ritonavir (RTV) and darunavir/ritonavir (DRV/r). 30 healthy volunteers received inhaled BDP 160 µg twice daily for 14 days and then randomized (1:1:1) into 3 groups: Group 1 (control) remained on BDP alone for 28 days; Group 2 received BDP + RTV 100 mg b.i.d for 28 days, and Group 3 received BDP + DRV/r 600/100 mg BID for 28 days. Geometric mean ratios (day 28: day 14) (90% CI) for 17-BMP area under the concentration-time curve in groups 1, 2, and 3, respectively, were 0.93 (0.81–1.06, p=0.27), 2.08 (1.52–2.65; p=0.006), and 0.89 (0.68–1.09; p=0.61). There were no significant reductions in serum cortisol levels within or between groups (p>0.05). DRV/r did not increase 17-BMP exposure, while RTV alone produced a statistically significant but clinically inconsequential 2-fold increase in 17-BMP exposure. Adrenal suppression was not observed in any of the study groups. These data suggest BDP can be safely coadministered with DRV/r and likely other RTV-boosted PIs (Boyd SD et al, 2013).

BDP contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

Beclometasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however, the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents (SmPC of Clenil Modulite, Chiesi Ltd, December 2018).

2.5.3.2 Pharmacodynamics

Mechanism of Action

Beclometasone dipropionate has high topical activity but low systemic activity. In asthmatic patients, the inhaled drug has little immunosuppressive effect and causes minimal changes in circulating leucocytes and eosinophils. Although antigen-induced type I immediate asthmatic and nasal reactions are not inhibited by prechallenge administration of single doses of beclometasone dipropionate, regular treatment for 1 week prior to antigen challenge inhibits such reactions in some patients. Substitution of inhaled BDP for oral maintenance corticosteroids in patients with asthma generally results in an improvement in adrenal function when the oral steroids have been administered daily (Brodgen RN et al, 2012).

A study was conducted to determine the effect of inhaled beclometasoneon on serum immunoglobulins. A total of 10 asthmatic patients (20% or greater reversibility in FEV_1 after Isoproterenol) and 10 age and sex matched controls were studied. Asthmatic patients were placed on inhaled beclometasone (400 µg/day in 4 divided doses) for at least 4 weeks. Serum IgG decreased significantly (10.2% $p \leq 0.018$). 8 of the 10 asthmatics had a net decrease in IgG, 1 remained unchanged and 1 had an increase of 4%. There was no significant change in other immunoglobulins. In summary, beclometasone administered in usual doses for 4 weeks appears to produce a significant decrease in serum IgG (Decotis BA et al, 1981).

A study examined the effect of inhaled beclometasone dipropionate aerosol on circulating leukocytes and on immunological measurements in normal adult subjects. Subjects inhaled either 400 µg or 1600 µg as a single dose. Among the 11 subjects who inhaled 400 µg, the total white blood cell count increased significantly at 6 hours. The total neutrophil count was increased significantly at 2, 4 and 6 hours. Total eosinophil counts and total lymphocyte counts were diminished but not significantly. Among the 5 subjects inhaling 1600 µg, similar findings were observed. 17 volunteers inhaled 200 µg of BDP qid for 24 hours. In addition to the above studies, T and B cell numbers were determined and lymphocyte transformation studies were performed. Although trends similar to those observed with single larger dose inhalations were seen, the changes were not statistically significant (Blaiss MS et al, 1982).

Pharmacodynamic studies

An open-label, non-randomized, crossover study compared the lung deposition of radiolabeled HFA-BDP with chlorofluorocarbon fluticasone propionate (CFC-FP) and CFC-BDP in 9 volunteers. On each study day, participants inhaled 1 or 2 puffs of ^{99}mTc-labeled HFA-BDP, CFC-FP, or CFC-BDP. All products delivered 50 µg/puff ex-valves. Radio-labeled HFA-BDP had a higher deposition in the lungs (53% ex-actuator) compared with CFC-FP (12 to 13%) and CFC-BDP (4%). HFA-BDP was deposited evenly throughout the lungs, while CFC-FP and CFC-BDP deposition was primarily in the large central and intermediate airways. Lung deposition was greater with HFA-BDP compared with CFC-FP and CFC-BDP. Deposition values appeared to be related to the particle size distribution of each inhaler, with the smaller

particles of HFA-BDP providing the greatest lung deposition and least oropharyngeal deposition (Leach CL et al, 2002).

Two phase I single-dose human deposition studies in healthy volunteers (n=6) showed that 55-60% of the HFA-BDP ex-actuator dose was deposited in the lungs, with 29-30% deposited in the oropharynx. CFC-BDP deposition was 4-7% in the lungs and 90-94% in the oropharynx. The pattern of deposition within the lung showed that HFA-BDP was spread diffusely throughout the lung airways. A second study with asthmatics (n=16) confirmed that 56% of the HFA-BDP dose was deposited in the airways, with 33% in the oropharynx. In conclusion, HFA-BDP deposition was much greater in the airways with a concomitant reduction in oropharyngeal deposition (Leach CL et al, 1998).

BDP is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to the active metabolite beclometasone- I7-monopropionate (B-I7-MP). The effect of BDP Modulite on the HPA axis has been compared with BDP-CFC 2000 µg in a crossover study conducted in I2 healthy volunteers. There was a similar reduction in serum cortisol (about 40% decrease) and in urinary cortisol excretion (45% decrease), for both treatments (Woodcock et al, 2002).

A single-blind trial of BDP was conducted in 16 patients suffering from bronchial asthma with or without chronic bronchitis. Patients received 3 randomized dosage regimens: 500, 1000 and 2000 µg/day, each for 4 weeks. The beta 2-adrenergic agonist response curve showed a dose-dependent increase in forced expiratory volume in 1s (FEV_1) which was not affected by different doses of BDP. A small but significant reduction in basal cortisol levels was observed after BDP 500 µg/day. There was no significant difference between the various doses of BDP in reducing cortisol level and stimulation with tetracosactide remained unchanged. The study showed a gradual, dose-dependent improvement in lung function, statistically significant for morning peak expiratory flow rate at BDP 2000 µg/day. Dyspnoea score and beta 2-agonist use decreased, reflecting the anti-asthmatic effects. An increase in total leukocyte count was observed, together with a decrease in the eosinophil count. Oral candidiasis was seen in 2 out of 16 patients (Molema J et al, 1988).

A double blind study evaluated the effect of a 2 months long treatment with inhaled BDP (300 µg/day) on methacholine responses in asthmatic children, during a period of maximal allergen exposure. Baseline values of methacholine PC_{20}-FEV_1 were 0.66 ± 0.22 mg/mL in 10 children treated with the active drug and 0.78 ± 0.21 mg/mL in 10 children treated with placebo. After 1 month of treatment PC_{20}-FEV_1 was 1.91 ± 0.64 and 0.80 ± 0.33 mg/mL, respectively, in the groups treated with beclometasone versus placebo. A statistically significant reduction in bronchial hyperreactivity (PC_{20}-FEV_1, 5.49 ± 1.86 mg/mL) but no systemic side effects were observed after 2 months of treatment with BDP. This is compared with a PC_{20}-FEV_1 of 1.38 ± 0.52 mg/mL in the placebo group. The results confirm the effect of inhaled corticosteroids in reducing bronchial hyperreactivity, even during a period of maximal allergen exposure (Boner AL et al, 1991).

A double-blind study examined adrenal effects after 14 days of dosing with HFA-BDP. A total of 43 steroid-naive asthmatic patients were randomised into 5 parallel groups and dosed every 12 h for 14 days with: HFA-placebo; 200, 400 or 800 µg/day HFA-BDP; or 800 µg/day CFC-BDP. After 2 weeks of dosing, the 24-h urinary free cortisol of all but 1 patient remained within the normal range, showing that all doses were well tolerated from a systemic safety perspective. The active HFA-BDP treatment groups showed a dose-related fall in 24-h urinary free cortisol. The greater systemic availability of HFA-BDP was still associated with adrenal effects comparable with that of the CFC formulation at the same dose (Harrison LI et al, 1999).

Pharmacodynamic interactions

A study determined whether montelukast provides additional clinical benefit to the effect of inhaled corticosteroids. A total of 642 patients with chronic asthma (FEV_1 50 to 85% of predicted value and at least a predefined level of asthma symptoms) incompletely controlled with inhaled beclometasone, 200 µg twice daily using a spacer device, during the 4-week run-in period were randomly allocated, in a double-blind, double-dummy manner to 1 of 4 treatment groups: (1) montelukast 10 mg plus continuing inhaled beclometasone; (2) placebo tablet plus continuing inhaled beclometasone; (3) montelukast 10 mg and inhaled placebo (after blind beclometasone removal); and (4) placebo tablet and inhaled placebo (after blind beclometasone removal). Montelukast provided significant clinical benefit in addition to inhaled beclometasone by improving FEV_1, daytime asthma symptom scores, and nocturnal awakenings. Blind removal of beclometasone in the presence of placebo tablets caused worsening of asthma control, demonstrating that patients received clinical benefit from inhaled corticosteroids. Blind removal of beclometasone in the presence of montelukast resulted in less asthma control but not to the level of the placebo group. In conclusion, montelukast provided additional asthma control to patients benefitting from, but incompletely controlled on, inhaled beclometasone (Laviolette M et al, 1999).

Table 3: Comparison study endpoints

	Beclometasone[*] (*n = 200*)	**Beclometasone + Montelukast[*] (*n = 193*)**	**p Value[‡]**
Primary			
Morning FEV_1, %[‡]	0.72 (−0.89, 2.33)	5.08 (3.43, 6.74)	< 0.001
Morning FEV_1, L[§]	−0.02 (−0.02, 0.06)	0.14 (0.10, 0.18)	< 0.001
Daytime asthma symptoms score[§]	−0.02 (−0.10, 0.06)	−0.13 (−0.22, −0.05)	0.041
Other			

	Beclometasone[*] (*n = 200*)	**Beclometasone + Montelukast[*] (*n = 193*)**	**p Value[‡]**
Total daily β-agonist use, % [‡]	6.04 (−3.78, 15.86)	−5.51 (−15.54, 4.52)	0.08
Morning PEFR, L/min [§]	2.65 (−1.31, 6.60)	10.41 (6.36, 14.47)	0.0041
Evening PEFR, L/min [§]	1.81 (−1.92, 5.55)	5.84 (2.00, 9.68)	0.11
Nocturnal awakenings, nights/wk[‖]	−0.45 (−0.85, −0.05)	−1.04 (−1.42, −0.67)	0.010
Asthma exacerbations, % days	17.92 (14.61, 21.23)	13.37 (9.97, 16.77)	0.041
Asthma attacks, % of patients	12.0	6.2	0.055
Physicians' global evaluation	2.40 (2.20, 2.60)	1.95 (1.74, 2.16)	0.001
Patients' global evaluation	1.86 (1.63, 2.10)	1.59 (1.35, 1.83)	0.085

[*] Least-square mean and the 95% CI.
[†]Comparison of beclometasone + montelukast with beclometasone groups.
[‡]Percentage change from baseline.
[§]Change from baseline.
[‖]Includes nocturnal asthmatic patients only: beclometasone, n = 74; montelukast + beclometasone, n = 85.

2.5.4 OVERVIEW OF EFFICACY

Clinical experience has shown that at doses of 200 to 600 µg daily, BDP inhaler is preferable to oral corticosteroids, because of lack of side-effects, when adult patients and children are inadequately controlled by maintenance corticosteroids.

Beclometasone dipropionate is indicated for the prophylactic management of mild, moderate, or severe asthma in adults or children. The starting dose of inhaled BDP should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained. The usual starting dose in adults including the elderly is 200 µg twice daily. In severe cases this may be increased to 600 to 800 µg daily. This may then be reduced when the patient's asthma has stabilised. The total daily dosage should be administered as 2 to 4 divided doses. BDP 200 µg is not recommended for children. The usual starting dose in children is 100 µg twice daily. Depending on the severity of asthma, the daily dose may be increased up to 400 µg administered in 2 to 4 divided doses.

Clinical experience with BDP inhaler in steroid-dependent asthmatic patients and in those not receiving systemic corticosteroids, indicates that BDP inhaler is preferable to oral corticosteroids when patients who are inadequately controlled by maintenance corticosteroids. Inhaled BDP can allow a worthwhile reduction in maintenance doses of systemic corticosteroids in many patients already receiving these drugs and can replace systemic steroids entirely in some patients, without causing a deterioration in their asthma, particularly when their initial dose of steroids is less than 10 mg daily of prednisone. Substitution should be attempted when the patient’s asthma is well controlled on usual doses of systemic steroids and full doses of other adjuvant therapy. Exacerbations of asthma should be controlled by immediate therapy with systemic corticosteroids.

Increasing the dose of BDP above 400 µg daily may benefit some selected patients who fail to respond to usual therapeutic doses. A dose of 800 µg daily may allow a greater reduction in maintenance doses of systemic steroids than 400 µg daily in patients whose initial dose of oral corticosteroids exceeds 16 mg daily (prednisone).

Therapeutic trials in children, suggest that adequate doses of BDP inhaler can replace corticosteroids or corticotrophin in most asthmatic children requiring maintenance therapy with these drugs. Many of the children treated with BDP inhaler have not been adequately controlled by sodium cromoglycate plus maintenance corticosteroids, but their asthma status has usually been maintained or sometimes improved when BDP aerosol has been substituted for systemic steroids. Substitution of BDP aerosol for systemic corticosteroids does not generally appear to result in either suppression or acceleration of growth or in obvious suppression of adrenal function.

The initial maintenance dose of corticosteroids seems to influence the ease with which these drugs can be withdrawn, particularly when fixed doses of 400 to 600 µg daily of BDP inhaler

have been used. Generally, withdrawal of maintenance corticosteroids in steroid-dependent asthmatics treated with BDP inhaler has been easier when the daily dose has been 10 mg or less of prednisone or its equivalent. The response to BDP may also be influenced by the initial lung function and by the inability to inhale effectively, and to some extent, by age. Overall response in children appears to be at least equal to that in adults (Brodgen R et al, 1975).

Summary of published clinical studies reported with beclometasone dipropionate on intended indications are presented below:

Mild to moderate asthma

Active Controlled Clinical Trials

A randomised single blind study was conducted to compare the clinical efficacy and of inhaled fluticasone propionate (FP), budesonide (BUD) and BDP in the treatment of bronchial asthma. A total of 42 adult asthmatics were randomly allocated to 3 treatment groups with 14 patients in each group. Group A received FP 200 µg b.i.d, Group B received BUD 400 µg b.i.d and Group C received BDP 400 µg b.i.d through MDI. After 12 weeks of therapy, it was observd that all treatments were effective in significantly reducing the symptoms and concomitant drug score in all the 3 groups. In Group A, the mean symptom score decreased from 38.4 to 8.2 and mean drug score decreased from 31.6 to 6.8. Similarly, in group B, the mean symptom score and mean drug score decreased from 47.9 to 13.8 and from 46.9 to 8.6. In group C these values decreased from 40.6 to 8.6 and from 34.6 to 6.7. Spirometry values also improved significantly in all the groups. It is therefore concluded that all the 3 treatments have similar efficacy in the treatment of bronchial asthma (Parakh U et al, 2004).

The dose-response effects of inhaled BDP and BUD administered b.i.d. with the aid of metered dose aerosols were studied in 128 patients suffering from asthma bronchiale. The study was designed as a multi-centre, double-blind, 4r-period cross-over study, followed by a single-blind double placebo period. BDP was administered in doses of 400 and 1000 µg, and BUD in doses of 400 and 800 µg. The results in terms of peak expiratory flow in the morning and evening, daily symptoms score and use of inhaled beta-2-agonists did not reveal any clinically significant differences between the drugs or between high (800 µg BUD, 1000 µg BDP) and low (400 µg BUD/BDP) doses. Adverse effects consisting mainly of oropharyngeal candidiasis, hoarseness and cough occurred in 54 of 468 treatment months (12 %) (Boe J et al, 1989).

A 12-week, parallel-group, multicenter study was conducted to compare the effect of HFA-BDP (400 µg/d) with that of CFC-BDP (800 µg/d) on asthma health-related quality of life. Following 7 to 12 days of prednisone (30 mg/d), 347 adults with moderate asthma were randomized to receive either 400 µg/d HFA-BDP, 800 µg/d CFC-BDP, or HFA placebo for 12 weeks. There was a deterioration in the AQLQ score (- 0.81) in the placebo group, and the difference between this and the stability observed in both the HFA-BDP group (+ 0.13) and the CFC-BDP group (- 0.03) was statistically significant ($p \leq 0.003$). The difference between the two active treatments was not significant ($p = 0.290$). The calculated number of patients who

needed to be treated in order to see a benefit in 1 patient (with the placebo as the standard treatment) was 2.4 for HFA-BDP and 3.0 for CFC-BDP. Only weak to moderate correlations were observed between changes in AQLQ scores and between asthma clinical status measures. In summary, HFA-BDP (400 µg/d) was as effective as CFC-BDP (800 µg/d) in sustaining improvements in asthma quality of life following withdrawal of 7 to 12 days of prednisone treatment in moderate asthma (Juniper EF et al, 1999).

A multicentric 2-phase trial was conducted in 55 asthmatics, previously treated with inhaled steroids. In the first phase (randomized, double-blind crossover study) 2 BDP inhalation aerosol preparations (MDI) were administered through collapsible spacer. In the second phase (open, randomized, parallel group comparison), 1 of the preparations was administered via collapsible and the other via traditional large volume spacer. The total daily dose of inhaled beclometasone was 1,000 µg. No statistically significant differences were found in PEFR or FEV_1 between the treatments during whole study. The asthma symptom scores were low as well as the use of concomitant inhaled sympathomimetics which indicates good and equal efficacy of the preparations. The MDI-spacer combinations were equally well tolerated (Laurikainen K et al, 1994).

Multicentre double-blind studies have been conducted to compare the therapeutic equivalence of a HFA-134a propellant-formulated BDP MDI with a CFC counterpart for the management of adult patients with all grades of asthma. Doses of 100 µg qds for 6 weeks were administered in a low dose study and in a high dose study 500 µg qds doses were given for 12 weeks. Both CFC and HFA-formulations of inhaled BDP produced similar and significant improvements in lung function and asthma symptoms. In the low dose study, baseline to endpoint FEV_1 increased from 2.2 ± 0.51 to 2.5 ± 0.81 (P = 0.0001) with BDP-CFC and from 2.2 ± 0.51 to 2.6 ±0.81 with BDP-HFA (P = 0.0001), with no significant difference between treatments. In the high dose study, corresponding increases were 2.1 ± 0.71 to 2.4 ± 0.91 (P = 0.0002) for BDP-CFC and 2.1 ± 0.71 to 2.3 ± 0.71 (P = 0.017) for BDP-HFA. PEF also improved similarly on both treatments in both studies. Both formulations were well tolerated with no difference in the pattern of adverse events, effect on serum cortisol or Candida colonization. These studies showed that, in the management of asthma, the HFA-formulated BDP MDI is equivalent to, and directly substitutable for, the older CFC-formulated product at the same dose (Milanowski et al, 1999).

Table 4: Lung function results (means & SD) (intent-to-treat populations)

	Low-dose study		**High-dose study**	
	BDP-CFC (n=57)	**BDP-HFA (n=56)**	**BDP-CFC (n=54)**	**BDP-HFA (n=54)**
FEV, (1)				
Baseline	2.2 ± 0.5	2.2 ± 0.5	2.1 ± 0.7	2.1 ± 0.7
Endpoint	2.5 ± 0.8**	2.6 ± 0.8**	2.4 ± 0.9**	2.3 ± 0.7**
Between treatment difference (HFA-CFC)	0.1		-0.1	

90% CI for difference	0.14, 0.35		- 0.34, 0.5	
Morning PEF (1 min - ‘)				
Baseline	391.5 ± 120.3	374.2 ± 113.3	353.6 ± 109.4	338.0 ± 100.8
Endpoint*	418.7 ± 118.5	412.9 ± 90.2	375.2 ± 107.7	364.3 ±103.9
Between treatment difference (HFA-CFC)	-5.8		-10.9	
90% CI for difference	- 15.7, 25.6		- 36.1, 19.2	

*, Average for last 3 weeks of treatment; **, P=0.0001

A randomized, multicentre, double-blind, double-dummy, parallel-group study demonstrated the equivalent efficacy for BDP 500 µg bid given via MDI with the HFA-134a propellant compared to a conventional CFC propellant in 116 adult patients with stable mild to moderate asthma ($FEV_1 \geq$ 60% of predicted normal). Patients were assigned to a 12-week treatment with the test drug. Equivalence between groups was demonstrated for the primary end-point morning peak expiratort flow rate (PEFR), as well as for evening PEFR and FEV_1. The other secondary pulmonary function tests measured showed a satisfactory asthma control, albeit without statistically significant differences between groups. Decreases in the use of rescue salbutamol and in clinical symptoms were also reported in both groups, with no differences between them. In conclusion, the BDP-HFA 134a formulation proved to be statistically equivalent to the standard BDP CFC product over 12 weeks in adult patients with mild to moderate asthma (Anderson et al, 2002).

A double-blind, double dummy, parallel-group study compared the efficacy of BDP 200 µg bid via MDI, using HFA-134a versus CFC as a propellant in 172 adult patients (86 in each group) with stable mild persistent asthma. In accordance with asthma of mild severity (FEV_1 predicted over 90% in both groups); a small improvement in lung function compared to baseline was seen for both treatments, significantly for FEV_1 in BDP HFA and mid expiratory flow at 50 % of the forced vital capacity (MEF_{50}) in both groups. The 2 formulations of BDP had similar efficacy for the primary outcome variable morning PEFR. There were small improvements in methacholine provocative dose (PD_{20}) and provocative concentration (PC_{20}) in both groups, with no significant difference between treatments. A total of 22 and 19 drug-related adverse events were reported in the BDP HFA and CFC groups, respectively; most events were of seasonal nature or were local effects due to the use of inhaled corticosteroids. It can be concluded that the formulation of BDP given via HFA-134a seems to provide similar asthma control, compared with the same low daily dose of the active drug delivered via CFC (Woodcock A et al, 2002).

A double-blind, multinational, multicentre, parallel-group study demonstrated the efficacy and tolerability of BDP aerosol spray 500 µg b.i.d. via a spacer device using a HFA-134a formulation or CFC propellant. 154 adult patients (77 in each group) with mild-to-moderate persistent asthma were randomised into 2 groups to receive the study treatment for duration of

12 weeks. Significant improvements over baseline were reported in both groups in terms of lung function, symptoms and use of rescue inhaled salbutamol. Equivalence between groups was demonstrated for the primary end-point morning PEFR, as well as for evening PEFR and FEV_1. No statistically significant differences in the comparisons between groups, except for forced expiratory flow at 25% FVC (FEF_{25}) were observed in any of the other efficacy variables. In conclusion, the BDP-HFA-134a formulation proved to be equivalent in efficacy and comparable in safety to the standard BDP-CFC product over 12 weeks in adult patients with mild-to-moderate persistent asthma (Vondra V et al, 2002).

Paediatrics

A double-blind, randomized, controlled study compared the efficacy of BDP and BUD by measuring the change in percentage predicted FEV_1 from baseline in children with mild persistent asthma. Of the 85 cases of mild persistent asthma, 42 received BUD while 43 received BDP at a dose of 400 µg/day using pressurized MDI with valved spacer for two months. There was a significant ($P < 0.05$) improvement in FEV_1 in BUD group (98.43 ± 4.63%) than in BDP group (95.65 ± 5.66%) at the end of 2 months of treatment. The mean symptom scores in BUD group (0.28 ± 1.22) and BDP group (0.43 ± 1.52) were comparable after two months. No side effects were seen in either group. FEV_1 was significantly greater in BUD group than BDP group. Improvement in symptoms and incidence of side effects were similar. The study indicated that both BDP and BUD can be used effectively in the management of children with mild persistent asthma (Singh A et al, 2016)

A double-blind, double-dummy, phase III study evaluated the efficacy and safety of BDP BAI and MDI versus placebo in 628 pediatrics patients ages 4-11 years with persistent asthma. Patients were randomly assigned (1:1:1: 1:1) to twice-daily BDP (BAI 80 µg/day, BAI 160 µg/day, MDI 80 µg/day, or MDI 160 µg/day) or to placebo. Percent predicted forced expiratory volume in 1 second (PPFEV1), area under the effect curve from 0 to 12 week showed numerical improvements from baseline in the BAI 80 µg/day and BAI 160 µg/day groups and MDI 80 µg/day and MDI 160 µg/day groups; however, these improvements were not significant versus placebo for any group after hierarchical testing was applied. Consistent improvements were noted in the active treatment groups versus placebo for the weekly average trough morning and evening PEFs, and with BAI 80 µg/day versus placebo for rescue albuterol/salbutamol use and the total daily asthma symptom score. Adverse events were comparable across the groups; the incidence of oral candidiasis ranged from 0.8 to 3.2% (Vanderwalker M et al, 2017).

A study demonstrated clinical equivalence of a standard 400 µg/d dose of inhaled BDP given via a HFA-134a propellant in 2 dose-units of 50 µg and 100 µg or with the CFC. A total of 218 children, ages 6-16, with mild to moderate persistent asthma in a stable phase, entered a 2-week run-in period and were then assigned to a 12-week treatment with 1 of the 3 treatment tests, following a double-blind, double-dummy (100 µg-dose strength as open arm), multicenter, parallel groups design. 207 patients entered the intent-to-treat (ITT) analysis and 181 completed the study period. Equivalence between the 3 treatment groups was demonstrated for the primary outcome measure morning PEFR as well as for the evening PEFR. No significant differences

among the groups were observed for the other efficacy variables, except for FEV_1 and forced vital capacity (FVC) (significantly higher increase in the 2 HFA groups than in the CFC group) and for the intake of salbutamol (non-significantly higher decrease of consumption in the CFC group). The 3 treatments also gave comparable results in terms of adverse drug reactions and of mean values of morning serum cortisol. No signs of marked cortisol decrease were reported in any of the 3 groups. The results of the study therefore show that the HFA-134a propellant can represent an alternative to the traditional CFCs in the delivery of 400 μg/d of BDP in mild to moderate asthmatic children (Lee TL et al, 2004).

A multicentered, double-blind, double-placebo, randomized, controlled trial was conducted to compare the benefits and adverse reactions of theophylline and BDP in the long-term control in 195 children between the ages of 6 and 16 years with mild to moderate asthma. Treatment with either BDP, 84 pg 4 times a day, or sustained-release theophylline administered twice daily in doses adjusted for optimum control of symptoms. Aerosol BDP and sustained-release theophylline were effective primary treatments for mild to moderate chronic asthma. Beclometasone resulted in comparable symptom control with less bronchodilator use and fewer courses of systemic steroids than theophylline. Side effects were observed significantly more frequently with theophylline than with BDP. Growth velocity suppression was noted with BDP and was more pronounced in boys. Suppression was not associated with alterations in cortisol measurements either at baseline or following stimulation. Thus, BDP is an effective therapy for mild to moderate asthma (Tinkleman DG et al, 1999).

A randomized clinical trial determined the effects of BDP inhaler and montelukast on the total serum level of immunoglobulin E (IgE) and childhood asthma control test (C-ACT) in asthmatic children aged 4 to 11 years with mild persistent asthma. Paients were randomly divided into beclometasone group (51 patients) and montelukast group (46 patients). There was a significant reduction in total serum IgE level (21% for montelukast group and 27% for beclometasone group) after 3 months of treatment compared to baseline IgE, and there was significant improvement in childhood C-ACT scores (16% for montelukast group and 24% for beclometasone group) after 3 months of treatment compared to the 1st month of treatment. There was a significant improvement in the beclometasone group compared to the montelukast group after 3 months of treatment. Both beclometasone and montelukast are effective controllers for asthma symptoms and reducing the total serum IgE level. Beclometasone is better than montelukast in improving C-ACT scores (Hasan AA et al, 2020).

Table 5: Effects of treatment with inhaled beclometasone and montelukast on total serum IgE levels in children with asthma

Group	Number of patients	Total serum IgE (IU/ml)		*P*
		Baseline	After treatment	
Beclomethasone	51	1540.5±639.2	1124.1±551.4	<0.01*
Montelukast	46	1414.9±945.9	1122.8±754.6	<0.01*
P		<0.05	<0.05	

*Significant differences

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Table 6: Effects of treatment with beclometasone and montelukast on childhood asthma control test scores in children with asthma during the treatment period

Group	Number of patients	C-ACT scores		*P*
		1st month of treatment	3rd month of treatment	
Beclomethasone	51	19.8±1	24.6±1.6	<0.01*
Montelukast	46	20.4±0.9	23.5±1.1	<0.01*
P		>0.05	<0.01*	

*Significant differences. C-ACT: Childhood asthma control test

A study compared the effects of salmeterol and beclometasone on lung function and symptoms in children with mild to moderate asthma. 67 children not treated with ICs were randomized in a double-blind parallel study either to salmeterol 50 µg b.i.d. or beclometasone 200 µg b.i.d. After 1 year, FEV_1 significantly increased in the beclometasone group, whereas in the salmeterol group there was a small reduction. Differences between groups were 14.2% and 7.0% for pre- and postbronchodilator FEV_1 values, respectively. PD_{20} methacholine decreased by 0.73 DD in the salmeterol group and increased by 2.02 DD in the beclometasone group. Morning and evening PEF and symptom scores improved in both groups, although more in the beclometasone group. Asthma exacerbations, for which prednisolone was needed, were more frequent in the salmeterol group (17 versus 2), as were the number of withdrawals due to exacerbations (6 versus 1). However, growth was significantly slower in the beclometasone group compared with that in the salmeterol group. In conclusion, treatment with a moderate dose of beclometasone is superior to salmeterol in children with mild to moderate asthma and recommends that salmeterol should not be used as monotherapy (Verberne AA et al, 1997).

Table 7: Percentage of patients showing an improvement in FEV_1 (pre- and postbronchodilator) and PD_{20} by treatment group

Treatment Week	6	12	18	24	30	36	42	48	54	Follow-up
Salmeterol										
FEV_1 pre	61	53	58	45	34	48	35	30	46	24
FEV_1 post		44		35		45		30		
PD_{20}	58		52		37		25		26	26
Beclometasone										
FEV_1 pre	91	86	88	85	88	88	85	85	88	77
FEV_1 post		74		79		79		67		
PD_{20}	77		76		76		82		81	77

Placebo Controlled Clinical Trials

A randomized, double-blind, double-dummy, placebo-controlled, multicenter trial was conducted in 328 adults with mild to moderately severe asthma (FEV_1 50% to 90% of predicted) while maintained on ICs to compare the efficacy and safety of BDP 336 µg/day administered by MDI alone, and triamcinolone acetonide (TA) 800 µg/day by MDI with a built-in tube extender in adults with persistent asthma. Mean increase in FEV_1 in the BDP group was statistically significantly greater than in the TA group on day 28. Throughout the study, BDP was statistically superior to TA with respect to mean change from baseline in total asthma symptom scores and for 3 of 8 weeks in reducing the mean average weekly use of rescue albuterol. BDP and TA were comparable in safety. In adult patients with mild to moderately severe persistent asthma, treatment with BDP consistently conferred greater improvement from baseline in mean FEV_1 than TA. This difference achieved statistical significance after 28 days of therapy but was not maintained to endpoint. Decreases in overall asthma symptom scores and in the use of rescue albuterol were statistically significantly greater for the BDP group compared with the TA group (Bronsky E et al, 1998).

A randomized, double-blind, placebo-controlled study of adult asthmatics compared the efficacy and safety of TA MDI with a built-in tube extender and BDP MDI without a spacer device were compared. The study was carried out in 339 patients, 18 to 65 years of age, with a documented history of bronchial asthma (FEV_1, 50 to 90% of predicted value) for ≥2 years who required ICs therapy. Patients were randomized to receive BDP 336 µg/d (4 puffs bid) plus TA placebo (4 puffs bid), TA 800 µg/d (4 puffs bid) plus BDP placebo (4 puffs bid), or TA and BDP placebos (4 puffs of each bid). At study end point, improvements in forced expiratory flow ($FEF_{25.75\%}$), clinic PEFR, and FVC were statistically significant for the active treatment groups compared with placebo. At end point, the mean difference between BDP and TA for mean

change in FEV_1 from baseline in the efficacy population was 0.02 and the 95% confidence interval was -0.11, 0.15. Treatment-related adverse events occurred with similar frequency in all patient groups-25.5% of placebo-treated patients, 22.3% of BDP patients, and 20.4% of TA patients. The study concluded that both active treatments were significantly more effective than placebo. All treatment groups were comparable in safety as measured by the incidence of adverse effects (Berkowitz R et al, 1998).

A 28-day, randomized, double-blind, double-dummy, placebo-controlled, multicenter study compared double-strength BDP (84 µg) MDI with BDP (42 µg) MDI in the treatment of asthma. A total of 423 patients aged 12 to 65 years (mean range, 34 to 36 years) with moderate asthma (FEV_1, 50 to 80% of predicted) who required long-term ICs were enrolled. Results showed that the 3 active treatments were significantly more effective ($p \leq 0.01$) than placebo at all time points in improving FEV_1. BDP 42 µg and BDP 84 µg were comparable to each other at every time point. Secondary pulmonary function tests (FVC, $FEF_{25-75\%}$, and PEFR) showed similar results. All 3 active treatments were well tolerated. In this well-controlled 28-day study, BDP 42µg and BDP 84µg were shown to be comparable in efficacy and safety (Nathan RA et al, 1997).

In a randomized, multicenter, double-blind, placebo-controlled, parallel-group study, 782 asthmatic patients (FEV_1 percent predicted values of between 50% and 85%) with weekly average β-agonist use of more than 2 puffs per day were randomized to receive montelukast (10 mg daily), beclometasone (200 µg twice daily), or placebo treatment for 6 weeks in a double-dummy fashion. The percentage of days of asthma control was almost identical between the montelukast and beclometasone groups (98% overlap in the distribution). Montelukast was at least equal to beclometasone, and both were greater than placebo on the basis of frequency of asthma attacks, asthma flare-ups, and rescue corticosteroid use. Beclometasone had a greater effect than montelukast and both treatments were better than placebo at improving FEV_1. In summary, montelukast was as effective as beclometasone, as judged by indices of clinical control other than FEV_1 (Israel E et al, 2002).

Table 8: Analysis of secondary end points

End point	Montelukast (n = 337)	Beclometasone (n = 329)	Placebo (n = 111)
FEV_1, L (change from baseline)	0.24 ± 0.03*†	0.38 ± 0.03*	0.10 ± 0.04
Daily β-agonist use, puffs/d (% change from baseline)	−30.3 ± 2.4*	−31.9 ± 2.5*	−9.7 ± 4.0
Patients without an asthma attack, %	97.0 ± 0.9*	96.1 ± 1.1	91.9 ± 2.6
Patients without asthma flare-up, %	22.0 ± 2.3*	17.6 ± 2.1*	8.1 ± 2.6
Patients with at least 1 sustained asthma control episode, %	55.5 ± 2.7*	59.3 ± 2.7*	44.1 ± 4.7
Patients without rescue corticosteroid, %	97.3 ± 0.8*	96.4 ± 1.0	92.8 ± 2.5

*$P \leq .05$ versus placebo. †$P \leq .01$ versus beclometasone. Values are given as means ± SE.

In a randomised double bind trial, 10 asthmatic patients received BDP (400 µg daily) or placebo for 4 weeks and then, after a 2-week washout period, they crossed over to the other treatment for 4 weeks. Treatment with beclometasone induced a small but significant reduction in bronchial responsiveness to histamine (p = 0.014). Although the improvement was too small to be considered of clinical significance, its importance lies in the mechanisms by which it was produced. Part of the improvement was related to improvement in airway caliber, but, even when the data was adjusted for this, there was still a significant difference between beclometasone and placebo treatment (p = 0.018). The results suggest that regular treatment with corticosteroids can alter bronchial responsiveness through mechanisms other than change in airway calibre (Ryan G et al, 1985).

A randomized, double-blind, double-dummy, parallel-group study compared the safety and efficacy of salmeterol xinafoate, BDP and placebo over a 6-month treatment period in patients with persistent asthma. Salmeterol (42 g twice daily), BDP (84 µg four times daily), or placebo was administered via MDI to 386 adolescent and adult inhaled corticosteroid-naive patients. Eligible patients demonstrated a FEV_1 from 65% to 90% of predicted values. There were few statistically significant differences between the two active treatments over 6 months of therapy. Asthma symptoms and lung function were significantly improved with both salmeterol and BDP compared with placebo. There were no significant differences among the treatment groups with respect to the distribution of asthma exacerbations over time. Both salmeterol and BDP significantly reduced bronchial hyperresponsiveness (BHR) compared with placebo. No rebound effect in BHR was seen upon cessation of any of the three treatment regimens. There were no clinically important differences in the safety profiles among the three treatments. Both salmeterol and BDP are effective and well-tolerated when administered for 6 months to inhaled corticosteroid-naive patients with persistent asthma (Nathan RA et al, 1999).

Paediatrics

A randomised, double-blind, crossover study was used to compare the effect of placebo, HFA-BDP 50 µg or 100 µg given q.d. on exercise-induced bronchoconstriction and exhaled nitric oxide (eNO). After a 14-day run-in, 25 children (5–14 yrs old) entered three 4-week treatment periods, separated by a 1-week washout. Significant treatment effects with no carry-over or period effects were seen for both eNO and maximum fall in FEV_1 after exercise. Differences were seen between placebo (fall in FEV_1=27.9%; eNO=14.4 parts per billion (ppb)) and either dose of HFA-BDP, but not between the two active doses (50 µg: fall in FEV_1=20.8%, eNO=9.3 ppb; 100 µg: fall in FEV_1=20.9%, eNO=8.9 ppb). In conclusion, low q.d. doses of hydrofluoroalkane-beclometasone dipropionate reduced exhaled nitric oxide and exercise-induced bronchoconstriction (Petersen R et al, 2004).

A randomized, double-blind, placebo-controlled, parallel-group, 1-year study was conducted in 241 children with clinically stable asthma and <1 month of prior glucocorticoid use. The authors

compared inhaled BDP (200 µg twice daily) with salmeterol xinafoate (50 µg twice daily) and placebo (lactose). During months 1 through 12 overall, beclometasone was associated with significantly less airway hyperresponsiveness than salmeterol or placebo. This effect was lost 2 weeks after treatment had been stopped. As compared with placebo, beclometasone was associated with less variability between morning and evening in the PEF, as was salmeterol. Beclometasone was also associated with a reduced need for albuterol as rescue therapy but salmeterol was not. During months 1 through 12, linear growth was 3.96 cm in the children receiving beclometasone, as compared with 5.40 cm in the salmeterol group and 5.04 cm in the placebo group. Height was not measured after treatment ended. In summary, beclometasone was effective in reducing airway hyperresponsiveness and in controlling symptoms of asthma, but it was associated with decreased linear growth (Simons FER et al, 1985).

Uncontrolled Clinical Trials

In a study, long term treatment of BDP was found to be effective in reducing symptoms of asthma in children. There was no measurable influence on pulmonary function. An 18-month follow-up did not show untoward side effects on adrenal function, growth, serum electrolytes, and hepatic and renal functions with a dose of 100 mug three times daily. The treatment predisposes to the colonization with *Candida albicans* in the oropharynx (Kerrebijn K et al, 1976).

Severe asthma

Active Controlled ClinicalTrials

A study compared the efficacy of FP and BDP in 306 patients with moderate to severe asthma in a double-blind, multicenter, cross-over study of 12-month duration. At randomization the current ICS was replaced by 500 microg BDP or 250 microg FP in accordance with previously taken 500 microg BDP or 400 microg budesonide (BUD). No significant differences between the two treatments regarding morning plasma cortisol, urinary excretion of calcium and hydroxyproline, FEV1, and PEFR were observed at any time point during the study. There was a similar antiasthmatic effect observed with the treatment (Pauwels RA et al 1998).

In a 26-week double-blind controlled study of 34 severe chronic patients whose asthma had been poorly controlled despite oral steroids, valuable clinical and pulmonary function improvement was derived by adding beclometasone aerosol to the prednisone regimen. The amount of improvement correlated linearly with beclometasone dosage over the range 200 to 1,600 µg/day. Success in achieving asymptomatic status was only 26% with the conventional 400 µg/day and 60 % at 1,600 µg/day. Oropharyngeal candidiasis was also dose-related but did not prohibit the use of high-dosage beclometasone. Respiratiory infections, physical signs, blood glucose, and electrolytes were unaffected by the drug. An individualized risk-benefit assessment seems a better basis for choosing an optimal beclometasone regimen for each patient than adherence to a conventionalized fixed dosage of 400 µg/day (Toogoogd JH et al, 1977).

The efficacy of budesonide (800 µg b.i.d.) and BDP (750 µg b.i.d.) in controlling the symptoms of asthma, pulmonary function, bronchial responsiveness to histamine, and adrenal function, was assessed in a double-blind, double-dummy cross-over study of 36 adult chronic asthmatic patients. Both treatment groups showed improvements from baseline in clinical assessment of lung function carried out after the first 6 weeks of treatment. No significant differences were seen throughout the entire 12 weeks' study, when comparing the effects of the treatments on FEV_1, FVC, PEF or the histamine PC_{20}. Asthma severity, symptom score and inhaled bronchodilator use showed the same results after both treatments. It was concluded that inhalations of budesonide and beclometasone dipropionate in high doses are equally potent in the treatment of severe asthma. There is no significant influence on the adrenal function and no significant side effects during a period equal to that of the present study (Svendsen UG et al 1992).

A six-month double-blind controlled trial compared a 2,000 µg per day dose of BDP aerosol with current upper level doses of 800 µg per day of the standard BDP, in asthmatics requiring oral corticosteroids in addition to BDP and bronchodilators. Both groups showed a'significant reduction in their oral steroid requirement during the study, with a 34% reduction in the lower dose group and a 57% reduction in the high dose BOP group while maintaining good symptomatic control of asthma; there was an associated improvement in baseline serum cortisol levels. Over the same period, the pulmonary function of the lower dose group showed significant worsening relative to that of the group receiving the high dose BDP which improved. There was no increase in dysphonia or oropharyngeal candidiasis among those using the concentrated BDP. High dose concentrated BDP appears to be a safe medication in long-term steroid-dependent asthma, and is effective in reducing dependence on the use of oral corticosteroid with associated improvement both in pulmonary and adrenal function (Tarlo SM et al, 1988).

A double-blind, double-dummy, multicentre, randomized, parallel-group study compared the efficacy and safety of high-dose corticosteroids given by nebulization or MDI in adult patients with severe asthma. Following a 2-week run-in period, 124 patients, aged 18-70 years, treated with high-dose inhaled steroids were randomized to 1 of 2 treatment groups for 12 weeks: BDP suspension for nebulization 3,000-4,000 µg/day b.i.d. given via a nebulizer (n = 63), or BDP spray 1,500-2000 µg/day b.i.d. given via a MDI plus spacer (BDP MDI) (n = 61). For the ITT population, in the BDP nebulization group mean morning PEFR increased statistically significantly from 308.7 ± 107.81/min to 3 19.2 ± 104.01/min while in the BDP MDI group the increase was from 301.5 ± 94.71/min to 309.3 ± 86.71/min. The 2 treatments were equally well tolerated. A total of 19 patients in each group reported adverse events during the treatment period, and these were generally mild-moderate in severity. In conclusion, the results of this study demonstrate that BDP suspension for nebulization 3,000-4,000 µg/day given via a nebulizer and BDP spray 1,500-2,000 µg/day given via an MDI plus spacer are equally effective, with an acceptable safety and tolerability profile, when used in steroid-dependent adult patients with moderate to severe asthma (Grzelewska-Rzymowska I et al, 2003).

An 8-week, randomised, double-blind crossover study was designed to test for equivalence of asthma control between an aerosol formulation of BDP incorporating a CFC free, HFA-134a and the conventional beclometasone aerosol formulated in CFC propellants in 68 asthmatic patients. All patients, previously stabilised on BDP, were randomised to receive the same dose of BDP from each of the study treatments. Statistically significant equivalence was demonstrated between HFA-BDP and CFC-BDP for asthma control parameters: FEV_1, morning and evening PEF, sleep disturbance, wheeze and cough, morning breathlessness and bronchodilator use. Such equivalence was also demonstrated for safety parameters. To conclude, it has been demonstrated that HFA-BDP achieves a level of asthma control that is clinically and statistically equivalent to CFC-BDP in terms of efficacy and safety, at total daily doses ranging from 200 µg to 600 µg in asthma patients previously stabilised on inhaled CFC-BDP (Dahl R et al, 1997).

A randomised, double dummy, single blind crossover study was performed in 18 subjects with chronic asthma, comparing the effect of 3 week's treatment with inhaled BDP, 1200 µg daily, and oral prednisone 12.5 mg daily. The mean FEV_1 at the start was 1.9 litres (56% predicted). There was no significant change in PD_{20} with prednisone treatment, the mean PD_{20} being 0.56 and 0.59 µmol before and after treatment. There was, however, a significant improvement in PD_{20} with BDP treatment, the geometric mean PD_{20} being 0.38 and 1.01 µmol before and after treatment (p less than 0.001). There was a small but significant improvement in mean FEV_1 after BDP treatment--from 1.9 to 2.2 litres--but no change after prednisone. Both medications produced significant and similar improvements in morning and evening airflometer readings, post-bronchodilator improvement, and diurnal variation. Thus at doses that had similar beneficial effects on lung function, BDP caused a significant improvement in bronchial hyperresponsiveness whereas prednisone caused no change. The superior topical anti-inflammatory effect of BDP may account for the different effects on bronchial hyperresponsiveness (Jenkins CR et al, 1988).

Paediatrics

A study described the long-term effect of oral montelukast, compared with inhaled corticosteroids in both adult and paediatric patients with chronic asthma. Patients received oral montelukast taken once daily (10 mg tablet for adults, 5 mg chewable tablet for paediatric patients) or ICs (beclometasone 200 microg twice daily for adults, beclometasone 100 microg or equivalent three times daily for children). Treatment with both montelukast and inhaled corticosteroids resulted in improvement in multiple parameters of asthma control. Improvements in daytime symptom scores were generally comparable among treatment groups. Both montelukast and ICs were effective in controlling chronic asthma; the relative effectiveness of montelukast and beclometasone were similar in open-label conditions (Williams B et al, 2001).

A single-blind crossover trial comparing BDP by inhalation with prednisolone by mouth in the treatment of asthmatic children over a period of 10 months is reported in 14 children aged between 9 and 16 years. All had severe chronic asthma requiring maintenance oral prednisolone

therapy in doses ranging from 2 to 7.5 mg/day. BDP given by inhalation in a dose of 400 µg/day was found to be a satisfactory alternative to prednisolone by mouth for controlling the symptoms of asthma (Mellis CM et al, 1976).

Placebo Controlled Clinical Trials

In a randomized double-blind 12-week trial of steroid-dependent patients with chronic asthma, 10 out of 17 patients receiving BDP aerosol in a total daily dose of 400 µg were able to discontinue systemic corticosteroid therapy successfully, compared to 2 out of 15 patients in the placebo group (P=0.002). At the end of the trial, the average 8 am plasma cortisol level in the group receiving beclometasone was more than twice the pretherapy value, whereas the level in the placebo group showed no significant change. There was no significant difference between the beclometasone group and the placebo group in the overall incidence of side effects related to the aerosol and the effects of systemic corticosteroid withdrawal. Oral candidiasis was not found in any patient receiving beclometasone dipropionate aerosol. Allergic nasal symptoms were disabling in many patients when the oral dosage of corticosteroids was tapered (Harvey LL et al,1976).

A randomized, double-blind, double-dummy, placebo-controlled, parallel-group, 12-week study compared the clinical benefit of montelukast 10 mg once daily; placebo; and inhaled beclometasone 200 µg twice daily administered with a spacer device in 895 patients with chronic asthma and an FEV_1 50% to 85% of predicted. Over the 12-week treatment period, the average percentage change from baseline in FEV_1 was 13.1% with beclometasone, 7.4% with montelukast, and 0.7% with placebo. The average change from baseline in daytime symptom score was 20.62 for beclometasone, 20.41 for montelukast, and 20.17 for placebo. Each agent improved PEFR and quality of life, reduced nocturnal awakenings and asthma attacks, increased the number of asthma-control days, and decreased the number of days with asthma exacerbations. Although beclometasone had a greater mean clinical benefit than montelukast, montelukast had a faster onset of action and a greater initial effect. The two agents caused similar decreases in peripheral blood eosinophil counts. Both agents had tolerability profiles similar to that of placebo over the 12-week study (Malmstrom, K et al, 1999).

The effect of inhaled BDP, 400 µg daily, was investigated in 31 prednisone-dependent asthmatics. In a double-blind noncrossover study of 25 patient's dependent on a daily prednisone dose of 17.5 mg or less, the dose of ingested prednisone was significantly diminished through the use of beclometasone as compared with placebo ($P < 0.001$). In a subsequent single-blind study of the 12 patients who had received placebo, a similar decrease in prednisone dose was possible when these patients received beclometasone. In all 25 patients the effect of beclometasone was maintained for 2 years; 9 came to require less beclometasone and 1 required more. In an additional single-blind study of 6 patients with severe asthma, dependent on prednisone in a dose of 20 to 25 mg/d, the response to beclometasone was more variable and less significant ($P < 0.01$). However, at 2 years there was no significant benefit ($P > 0.05$) and there were two treatment failures. In patients in whom reduction of dose or discontinuation of prednisone was possible plasma cortisol values before and after corticotropin

administration increased significantly (P < 0.001). Prednisone reduction was associated with the appearance of mild musculoskeletal steroid-withdrawal symptoms of short duration in 15 patients, and recurrence of symptoms of rhinitis in 15 patients. Side effects of beclometasone included episodes of hoarseness in 6 and easily treated oropharyngeal Candida albicans infection in 14 (Kerigan AT et al, 1977).

In a double-blind, randomized study, 93 corticosteriod-independent patients with chronic bronchial asthma were treated with either BDP aerosol at 400 µg per day or its vehicle for 4 weeks to determine and compare the effectiveness and safety of the preparations. Evaluations made before, at weekly intervals during, and 1 week after treatment indicated that BDP aerosol was superior to its vehicle in improving FVC, FEV_1, $FEF_{25\%-75\%}$, and clinical signs and symptoms, and in the overall evolutions by both the investigators and, the patients. Plasma cortisol levels measured at the end of the 2nd and 4th weeks were not substantially diferent from those before treatment in either group. No significant side effects or abnormalities in laboratory results were noted (Vogt F et al, 1976).

Paediatrics

A total of 22 children with chronic asthma requiring daily administration of bronchodilators but not steroids were administered 400 µg of BDP or a placebo (vehicle) in a double-blind crossover study. The experimental design consisted of 4 study periods (four weeks each): (1) baseline, (2) BDP or placebo treatment, (3) washout, (4) BDP or placebo treatment. The mean weekly symptom score was 76.5 ± 10.8 (mean ± SE) during placebo compared to 21.3 ± 5.3 during BDP therapy ($P < .005$). The number of attacks per week was 7.1 ± 1.4 in those receiving placebo and 1.6 ± 0.6 in those receiving BDP ($P < .005$). Mean medication score was 39.6 ± 3.6 during placebo and 21.6 ± 1.3 during BDP therapy ($P < .005$). Mean weekly average wright peak flow (WPF) measurements increased 33% with BDP therapy compared to placebo. 80 % of patients showed an increase in FEV_1 and in maximum MEF during BDP therapy. All throat cultures were negative. No pituitary-adrenal function suppression was noted in any of the parameters studied.BDP was shown to be highly effective in controlling asthma and produced no adverse effects (Klein R et al, 1977).

Uncontrolled clinical trials

In a study, 29 of 33 steroid-dependent asthmatic patients received 18 months of therapy with BDP. 26 of 29 patients noted a marked improvement in their asthma; 3 of 29 described an indeterminate response. A statistically significant improvement in many of the symptoms, the plasma cortisol level, the first-second FEV and the $FEF_{50\%}$ was present only at the end of 3 months of therapy with BDP. Steroid-withdrawal symptoms, particularly those related to the nose and sinuses, were initially troublesome but decreased with the passage of time. No oropharyngeal fungal infections were observed. At a dose below the hypothalamic-pituitary-adrenal suppressive level, therapy with BDP appears to be safe and effective for treating patients with steroid-dependent asthma (Kass I et al, 1977).

Beclometasone dipropionate was used in pressurized aerosols for the treatment of 60 cases of chronic allergic asthma for up to 15 months. 28 out of 37 cases were transferred to this treatment after being dependent on oral steroids for up to 16 years. 19 out of 23 other asthmatics not dependent on steroids were also completely controlled. No biochemical evidence of adrenal suppression was found. Steroid withdrawal symptoms were often a problem, suggesting absence of systemic absorption (Brown HM et al, 1972).

A clinical trial of BDP aerosol therapy in 41 patients with asthma studied the extent to which this therapy could replace systemic corticosteroid therapy. In a clinical trial of 41 patients with perennial asthma, the 10 who had not required long-term corticosteroid therapy improved symptomatically and in pulmonary function. Of the 31 who had required prolonged systemic corticosteroid therapy 12 were able to discontinue oral prednisone therapy, 15 were able to decrease the maintenance dose of prednisone and only 4 were unable to decrease the dose; all maintained satisfactory lung function and some showed improvement. Discontinuation of systemic corticosteroid therapy was accomplished more readily in patients whose daily maintenance dose was less than 15 mg and who had been taking the drug for less than 3 years. Side effects consisted of a "dry throat" in 7 patients, 2 of whom had throat infections with Candida albicans. Recurrence of rhinitis after discontinuation or reduction of systemic corticosteroid therapy was noted in 11 patients (Champion P et al, 1975).

A double-blind cross-over trial lasting 4 weeks of BDP aerosol in 39 children and young people with asthma already on oral corticosteroid treatment showed a significant beneficial effect which in most cases was maintained on continued open treatment for a further 4 weeks. An overall assessment based on several clinical observations and measurements suggested that 24 (62%) were improved while having BDP. After a month on known BDP, 15 patients had stopped oral corticosteroid treatment and 5 had reduced the dose without relapse. Response to treatment was not related to total IgE levels. No serious side effects were noted (Smith J et al, 1973).

The effects of BDP aerosol (400 µg/day) on clinical course, pulmonary function, and pituitary-adrenal function was studied in 34 steroid-dependent asthmatic children. After 12 weeks of BDP therapy, 30 of 34 patients no longer required prednisone. Mean weekly symptom and medication scores and the number of attacks decreased significantly. A significant improvement was demonstrated in the patients' peak flow, FEV_1 and MEF. 30 of the 34 patients initially had abnormal metyrapone responses, 28 had abnormal diurnal cortisol levels, whereas only 14 had abnormal IV corticotropinresponse tests. Although significant improvement was noted in the mean metyrapone and diurnal cortisol tests, only partial recovery of pituitary-adrenal function was observed in 20 patients, complete recovery in 5, and no change in 9. BDP was found to be therapeutically superior to oral steroids in the group of steroid-dependent asthmatic children and produced no serious adverse effects (Kershnar et al, 1978).

Meta-analysis and systemic review

The main objective of the clinical development programme for BDP Modulite, a non-extra fine formulation of BDP in HFA, has been to demonstrate therapeutic equivalence compared with standard BDP CFC products at the recommended posology (delivered dose and patient population). A total of 1158 asthmatic patients were included in 5 clinical studies and 658 patients were treated with BDP Modulite. 4 studies were undertaken in mild or moderate-to-severe asthmatic adults; while 1 study was carried out in children. The duration of treatment were 12 weeks in 3 studies and 6 weeks in the other 2 studies. A range of doses of BDP Modulite from 200 µg bid up to I500 µg bid was evaluated against CFC comparators. The primary efficacy variable in all studies was morning PEFR while secondary variables included other lung function parameters, symptom scores and salbutamol use. All studies demonstrated equivalence of efficacy for morning PEFR for BDP Modulite versus BDP-CFC.The secondary outcome variables also consistently support similar efficacy of the 2 products. The safety and tolerability profile for BDP Modulite was similar to BDP-CFC; the incidence of adverse events was comparable between treatments and plasma and urinary cortisol were generally unchanged in patients receiving 1000 µg/day for 6- 12 weeks. In conclusion, the results of the clinical studies with BDP Modulite show that this new HFA formulation allows a seamless transition to CFC-free BDF: thus simplifying the changeover (Bousquet et al 2002).

Posolgy and method of administration

Posology

Beclometasone dipropionate is for inhalation use only. The Volumatic™ spacer device may be used by patients who have difficulty synchronising aerosol actuation with inspiration of breath. The starting dose of inhaled BDP should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained.

Adults (including the elderly): The usual starting dose is 200 µg twice daily. In severe cases this may be increased to 600 to 800 µg daily. This may then be reduced when the patient's asthma has stabilised. The total daily dosage should be administered as 2 to 4 divided doses.

The Volumatic™ spacer device must always be used when BDP is administered to adults and adolescents 16 years of age and older taking total daily doses of 1000 µg or greater.

Children: The usual starting dose is 100 µg twice daily. Depending on the severity of asthma, the daily dose may be increased up to 400 µg administered in 2 to 4 divided doses.

Beclometasone dipropionate must always be used with the Volumatic™ spacer device when administered to children and adolescents 15 years of age and under, whatever dose has been prescribed.

Patients with hepatic or renal impairment: No dosage adjustment is needed in patients with hepatic or renal impairment.

Method of Administration

The aerosol spray is inhaled through the mouth into the lungs. The correct administration is essential for successful therapy. The patient must be instructed on how to use BDP correctly and advised to read and follow the instructions printed on the Patient Information Leaflet carefully.

2.5.5 OVERVIEW OF SAFETY

The safety profile of inhaled beclometasoneas discussed below is based on collation of data from various clinical studies that have been discussed under different sections of this report and information available in the published domain.

The effect of inhaled BDP, 400 µg daily, was investigated in 31 prednisone-dependent asthmatics. Episodic hoarseness was a complaint made by 6 patients and oral *Candida Albican* infection occurred in 14 patients. It usually affected the tongue or soft palate and responded in all cases to treatment with nystatin,100000 IU 3 times daily, held briefly in the mouth and then swallowed (Kerigan AT et al, 1977).

A randomized, multicentre, double-blind, double-dummy, parallel-group study demonstrated the reported adverse events in 81.4% of patients in the BDP HFA group and in 82.5% in the CFC group. There were 73 and 59 adverse drug reactions in the 2 groups, respectively; the difference was mainly due to differences in taste. No drug-related serious adverse events were reported in either group. No difference was seen for morning serum cortisol between baseline and end of treatment, or between groups (Anderson PB et al, 2002).

A double-blind, double dummy, parallel-group study compared the safety of BDP 200 µg bid via MDI, using HFA-134a versus CFC as a propellant in 172 adult patients (86 in each group) with stable mild persistent asthma. The number of drug-related adverse reactions (adverse events with a definite, probable or possible relationship with the test treatment) was 22 in the BDP HFA group and 19 in the BDP CFC group. The majority of ADRs were due to upper respiratory infections, but local events (hoarseness, cough, sore throat and oral candida) and episodes of headache were also reported in both groups in a similar extent. No serious adverse events occurred at any time in either group. No significant changes within or between groups were reported for vital signs, except for heart rate, where an increase was reported at the end of treatment in both groups; these changes had, however, no clinical relevance (Woodcock A et al, 2002).

Multicentre double-blind studies have been conducted to compare the therapeutic equivalence of a HFA-134a propellant-formulated BDP MDI with a CFC counterpart for the management of adult patients with all grades of asthma. In these studies, majority of adverse events were mild or moderate in severity and did not result in treatment withdrawal. The most commonly reported adverse events included candidiasis, infection, pharyngitis, cough, nausea and dyspepsia; there was no preponderance of any one type of adverse event in either group. The majority were not considered treatment-related by the reporting investigator. Although oral candidiasis comprised 20% of overall adverse events in the high-dose study, a quarter of these patients had this as a pre-existing condition. In 22 patients with throat swabs positive for *Candida albicans* at study entry, these resolved while under treatment, while 27 developed positive throat swabs at some stage during the study. 3 patients in the low-dose study and 5 patients in the high-dose study were withdrawn due to a variety of non-serious adverse events. 2 patients (one in each study) experienced intercurrent exacerbations of asthma after 2 and

4 weeks in the study, resulting in their hospitalization and withdrawal from the study. These patients recovered fully after additional treatment. In the investigators' opinions, these were unlikely to be related to study treatment; one case was almost certainly due to bronchitis (Milanoswki et al, 1999).

Table 9: Incidence of most commonly reported adverse events

	Low-dose study		**High-dose study**	
	BDP-CFC (n=60)	**BDP-HFA (n=59)**	**BDP-CFC (n=59)**	**BDP-HFA (n=60)**
Patients reporting any adverse event	36 (60%)	34 (58%)	51 (86%)	44 (73%)
Candidiasis	9 (15%)	7 (12%)	35 (59%)	28 (47%)
Infection	5 (8%)	6 (10%)	12 (20%)	6 (10%)
Pharyngitis	11 (18%)	6 (10%)	14 (24%)	9 (15%)
Cough	2 (3%)	3 (5%)	10 (1,7%)	3 (5%)
Nausea	3 (5%)	3 (5%)	3 (5%)	2 (3%)
Dyspepsia	4 (7%)	1(2%)	-	-

The most commonly reported adverse events included nausea and dyspepsia; there was no preponderance of any one type of adverse event in either group (Milanoswki et al, 1999).

Table 10: Adverse events

System organ Class	**Adverse Reaction**	**Adverse Reaction**
Infections and Infestations	Oral candidiasis (of the mouth and throat)	Very Common
Immune System Disorders	Hypersensitivity reaction with the following manifestations:	
	Rash, urticaria, pruritus, erythema	Uncommon
	Oedema of the eyes, face, lips and throat	Very rare
Endocrine Disorders	Adrenal suppression*, growth retardation* (in children and adolescents), bone density decreased*	Very Rare

Psychiatric Disorders	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural disorders (predominantly in children)	Unknown
Nervous System Disorders	Headache	Uncommon
Gastrointestinal Disorders	Nausea	Unknown
Eye Disorders	Cataract*, glaucoma*	Very rare
	Vision, blurred	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Hoarseness, throat irritation	Common
	Paradoxial bronchospasm, wheezing, dyspnoea, cough	Very rare

A double-blind, multinational, multicentre, parallel-group study demonstrated the tolerability of BDP aerosol spray 500 µg b.i.d. via a spacer device using a HFA-134a formulation or CFC propellant. 154 adult patients (77 in each group) with mild-to-moderate persistent asthma were randomised into 2 groups to receive the study treatment for duration of 12 weeks. Adverse events were reported in 31% of patients in the BDP-HFA group and in 32% in the CFC group. Adverse drug reactions were 4 and 2 in the two groups, respectively. No drug-related serious adverse events were reported in either of the groups. No signs of relevant adrenal suppression were observed in both groups: 2 patients in each group had final values below the normal range (Vondra V et al, 2002).

A total of 642 patients with chronic asthma (FEV_1 50 to 85% of predicted value and at least a predefined level of asthma symptoms) incompletely controlled with inhaled beclometasone, 200 µg twice daily using a spacer device, during the 4-week run-in period were randomly allocated, in a double-blind, double-dummy manner to 1 of 4 treatment groups: (1) montelukast 10 mg plus continuing inhaled beclometasone; (2) placebo tablet plus continuing inhaled beclometasone; (3) montelukast 10 mg and inhaled placebo (after blind beclometasone removal); and (4) placebo tablet and inhaled placebo (after blind beclometasone removal).The most commonly reported adverse experiences were upper respiratory tract infection, worsening asthma, and headache. Laboratory adverse experiences occurred with similar frequency across the 4 treatment groups. There were no patients who discontinued because of a laboratory abnormality. The incidence of elevated alanine aminotransaminase (ALT) and aspartame aminotransaminase (AST) were similar among the treatment groups; changes were generally transient and self-limited while continuing study medication (Laviolette M et al, 1999).

Table 11: Most common clinical adverse experiences occurring in > 6% of patients (% of randomly allocated patients) located

	Placebo (*n = 48*)	**Montelukast (*n = 201*)**	**Beclometasone (*n = 200*)**	**Beclometasone + Montelukast (*n = 193*)**
Asthenia/fatigue	6.3	1.0	0.5	1.6
Nausea	0	6.0	5.5	2.6
Headache	12.5	25.9	21.0	25.9
Worsening asthma	41.7	37.3	20.0	11.9
Bronchitis	8.3	3.5	2.0	2.6
Cough	6.3	5.5	2.5	4.1
Upper respiratory infection	39.6	35.8	39.5	36.3
Influenza	6.3	7.5	5.5	5.7
Pharyngitis	4.2	6.0	8.0	5.2
Sinusitis	4.2	6.0	4.5	4.1
Rash	6.3	3.5	1.5	0.5

Percentage of patients per treatment group is reported

The safety and effectiveness of inhaled beclometasone was established in a double-blind cross-over trial in non-steroid-dependent asthmatic patients. At a dosage of 400 to 800 µg/day for 3 months, there was no evidence of suppression of hypothalamic-pituitary-adrenal function. A 12-month follow-up study of 120 patients using steroid aerosols (betamethasone valerate or BDP) indicated that tolerance does not develop and that a daily maintenance dose of 200 µg/day was adequate in most patients. Temporary lack of response was observed during episodes of sputum production or of heavy exposure to antigen. There were no observed side effects other than fungal infections of the respiratory tract. However, the incidence of candidiasis of the pharynx (13%) and particularly of the larynx (5%) in apparently immunologically normal patients was disturbing. These infections were not seen in patients taking 200 µg/day. Though there is yet no evidence that fungal infections associated with steroid aerosols may penetrate the trachea and bronchi the possibility of this indicates that caution should be exercised in their use, particularly in long-term high dosage (McAllen MK et al, 1974).

A study compared the effects of salmeterol and beclometasone on lung function and symptoms in children with mild to moderate asthma. 67 children not treated with ICs were randomized in a double-blind parallel study either to salmeterol 50 µg b.i.d. or beclometasone 200 µg b.i.d. The mean increase in height was 6.1 cm (95% CI 5.3; 6.9) in the salmeterol treated group, compared with 4.7 cm (95% CI 4.0; 5.3) in the beclometasone treated group. Standard deviation scores (SDS) showed a change of 20.03 SDS in the patients treated with salmeterol compared

to 20.28 SDS in the patients treated with beclometasone. No interaction was found with gender. A significant interaction was found with puberty; the mean difference in SDS between groups was 20.10 (95% CI 20.29; 0.10) for patients with puberty stages 2 and more and 20.37 (95% CI 20.58; 20.16) for prepubertal patients (Verberne AA et al, 1997).

Table 12: Most common reported adverse events during the treatment period

	Salmeterol	**Beclometasone**
Number of patients	32	35
Number of patients with any adverse event	30 (94%)	31 (89%)
Number of patients with:		
Asthma	18 (56%)	3 (9%)
Rhinitis	9 (28%)	5 (14%)
Fever	8 (25%)	4 (11%)
Nausea and vomiting	7 (22%)	4 (11%)
Headache	6 (19%)	11 (31%)
malaise and fatigue	4 (13%)	10 (29%)
viral infections	4 (13%)	3 (9%)
breathing disorders	4 (13%)	3 (9%)
Cough	3 (9%)	8 (23%)
upper respiratory tract infection	3 (9%)	5 (14%)
viral respiratory infection	2 (6%)	10 (29%)
throat irritation	2 (6%)	3 (9%)
Injuries	0	4 (11%)

A double-blind study examined adrenal effects after 14 days of dosing with HFA-BDP. A total of 43 steroid-naïve asthmatic patients were randomised into 5 parallel groups and dosed every 12 h for 14 days with: HFA-placebo; 200, 400 or 800 μg day^{-1} HFA-BDP; or 800 μg day^{-1} CFC-BDP. After 2 weeks of dosing, the 24-h urinary free cortisol of all but 1 patient remained within the normal range, showing that all doses were well tolerated from a systemic safety perspective. The active HFA-BDP treatment groups showed a dose-related fall in 24-h urinary free cortisol. A non-linear correlation between 24-h urinary free cortisol and the PK parameters was observed, reflecting smaller changes in 24-h urinary free cortisol than in pharmacokinetics as the dose was increased. The greater systemic availability of HFA-beclometasone dipropionate was still associated with adrenal effects comparable with that of the CFC formulation at the same dose (Harrison LI et al, 1999).

A randomized, single-blind, placebo-controlled, 4-period cross-over trial was conducted in asthmatic patients who received 8 inhalations of 4 treatment regimens (HFA-134a BDP, 1600 µg total dose; CFC-11/12 BDP, 2000 mg total dose; HFA-134a placebo and CFC-11/12 placebo) in random order over 4 study days. FEV_1) was measured before and 2, 10, 20,40 and 60 min after inhalation of the study treatments. The number of coughs was counted from the start of the first inhalation to 60 s after the last inhalation. There were no statistically significant differences between the treatment groups for changes in FEV, for the number of coughs or for the occurrence or severity of bronchoconstriction. In asthmatic patients with holding bronchodilators, the HFA-134a BDP propellant system proved as safe and was as well tolerated as the current CFC-11/12 BDP system. The two propellant systems without active drug were also equally well tolerated (Ayres JG et al, 1999).

An analysis summarized studies comparing attained heights with expected heights of children with asthma treated with inhaled or oral corticosteroids. The results of these studies revealed a significant but small tendency for corticosteroid therapy in general to be associated with diminished final height. A significant moderate tendency was observed for inhaled beclomethansone dipropionate therapy to be associated with attaining *normal* stature. There was no statistical evidence for beclometasone dipropionate therapy to be associated with growth impairment at higher doses, for longer therapy durations, or among patients with more severe asthma (Allen DB et al, 1994).

A study was conducted to determine whether any systemic absorption following the inhalation of beclometasone was a result of drug being absorbed from the lung (inhaled fraction) or the GI tract (swallowed fraction), the authors studied normal subjects after the inhalation or swallowing of 2 mg beclometasone dipropionate. Systemic activity was assessed using early morning cortisol suppression. Both inhaled and swallowed fractions produced significant systemic activity, the degree of which depended on the inhaler device used. Systemic activity was greater using a dry powder inhaler (52%) than using a MDI with a large volume spacer (28%). These findings suggest that to limit potential adverse effects from high-dose BDP it is better to use a metered dose aerosol with large volume spacer than a dry powder (Trescoli C et al, 1998).

A meta-analysis assessed whether increasing the dose of ICS is associated with slower linear growth, weight gain and skeletal maturation in children with asthma. Among 22 eligible trials, 17 group comparisons were derived from 10 trials (3394 children with mild to moderate asthma), measured growth and contributed data to the meta-analysis. Trials used ICS (beclometasone, budesonide, ciclesonide, fluticasone or mometasone) as monotherapy or as combination therapy with a long-acting beta2-agonist and generally compared low (50 to 100 µg) versus low to medium (200 µg) doses of HFA-BDP equivalent over 12 to 52 weeks. In prepubescent school-aged children with mild to moderate persistent asthma, a small but statistically significant group difference in growth velocity was observed between low doses of ICS and low to medium doses of HFA-beclometasone equivalent, favouring the use of low-dose ICS. No apparent difference in the magnitude of effect was associated with three molecules

reporting 1-year growth velocity, namely, mometasone, ciclesonide and fluticasone. Findings support use of the minimal effective ICS dose in children with asthma (Pruteanu AI, 2004).
A study compared the effect alternate-day prednisone and inhaled BDP on hypothalamic-pituitary-adrenal function in 20 children with chronic asthma. Patients were evaluated while receiving 20 to 40 mg of prednisone on alternate mornings or 400 to 800 µg per day of inhaled BDP in divided daily doses; seven children requiring only non-corticosteroid medication served as controls. Early-morning serum cortisol concentration, urinary free-cortisol excretion and the 11-desoxycortisol response to metyrapone were decreased to a similar degree among children receiving both corticosteroid regimens in comparison with the control patients and were lowest when alternate-day prednisone and inhaled BDP were given together. Thus, inhaled BDP appears similar to alternate-day prednisone in its effect on hypothalamic-pituitary-adrenal function when used alone; the effect is additive when the 2 are used together (Wyatt R et al, 1978).

Overdose

Acute: Inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action. In these patient's treatment should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

Chronic: Use of inhaled beclometasone dipropionate in daily doses in excess of 1,500 µg over prolonged periods may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control asthma (SmPC of Clenil Modulite, Chiesi Ltd, December 2018).

Contraindications

Hypersensitivity to the active substance or to any of the excipients (SmPC of Clenil Modulite, Chiesi Ltd, December 2018).

Special warnings and precautions for use

Patients should be properly instructed on the use of the inhaler to ensure that the drug reaches the target areas within the lungs. Patients should also be informed that BDP should be used on a regular basis, even when they are asymptomatic.

Beclometasone dipropionate does not provide relief of acute asthma symptoms, which require a short-acting inhaled bronchodilator. Patients should have relief medication available.

Severe asthma requires regular medical assessment, including lung-function testing, as there is a risk of severe attacks and even death. Patients should be instructed to seek medical attention if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required as this may indicate deterioration of asthma control. If this occurs, patients

should be assessed and the need for increased anti-inflammatory therapy considered (eg. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Severe exacerbations of asthma must be treated in the usual way, ie. by increasing the dose of inhaled BDP, giving a systemic steroid if necessary, and/or an appropriate antibiotic if there is an infection, together with β-agonist therapy. Treatment with BDP should not be stopped abruptly (SmPC of Clenil Modulite, Chiesi Ltd, December 2018).

Systemic effects of inhaled corticosteroids

A systematic review and meta-analysis was conducted to appraise the data on systemic adverse effects of inhaled corticosteroids. Marked adrenal suppression occurs with high doses of ICs above 1.5 mg/d although there is a considerable degree of interindividual susceptibility. Meta-analysis showed significantly greater potency for dose-related adrenal suppression. ICs in doses above 1.5 mg/d may be associated with a significant reduction in bone density. Although medium-term growth studies showed suppressive effects with 400 µg/d BDP, there was no evidence to support any significant effects on final adult height. Long-term, high-dose ICs exposure increases the risk for posterior subcapsular cataracts, and, to a much lesser degree, the risk for ocular hypertension and glaucoma. Skin bruising is most likely to occur with high-dose exposure, which correlates with the degree of adrenal suppression. All ICs exhibit dose-related systemic adverse effects, although these are less than with a comparable dose of oral corticosteroids. The long-term systemic burden will be minimized by always trying to achieve the lowest possible maintenance dose that is associated with optimal asthmatic control and quality of life (Lipworth BJ et al, 1999).

Endocrine disorders

A study was undertaken to evaluate the effects of inhaled BDP (400 and 800 µg) over a period of 6 months on the hypothalamo-pituitary-adrenal axis (HPA) suppression. Assessment of the HPA function was carried out by tetracosactrin test at time zero, (before start of treatment), 3 months, and 6 months. There were 7 patients who were inhaling BDP in a dose of 400 µg/day and another 7 patients were taking the same drug in a dose of 800 µg/day. There was no side effect of the drug in any patient except in one patient who had dysphonia. The mean basal cortisol levels were normal in all the subjects at 0, 3 and 6 months of therapy. Tetracosactrin stimulation test was also normal in all patients at all the times who were receiving the dose of 400 µg/day. However, 1 patient (14%) receiving 800 µg/day had HPA axis suppression at 6 months. 2 patients in this group also had low basal cortisol levels. There was no clinical evidence of such suppression/deficiency. BDP in a dose of 800 µg/day may suppress the HPA if used for long periods (6 months). However, this may not have any clinical significance (Gupta D et al, 2000).

In a prospective, randomized and double-blind study, 23 steroid-naive children with moderately severe asthma, aged 5–10 yrs, were allocated either BDP (400 µg/day) or FP (200 µg/day) using a MDI with a spacer. Bone mineral density (BMD) was measured at each visit. None of the

markers of bone turnover showed any change during the study period. BMD increased at normal rates with age. Serum cortisol significantly decreased on BDP, but not on FP. A significant difference in growth rates was found between the groups, with a slower rate of growth towards the end of the observation period in the BDP group. In conclusion when taken in a relatively modest dose over a period of time, beclometasone dipropionate had significant effects on the HPA and statural growth in childhood asthma (Rao R et al, 1999).

A randomized, double-blind, placebo-controlled, community-based study evaluated the effect of inhaled BDP 400 µg/day for 7 months on the linear growth and adrenal function of 94 children 7 to 9 year of age. Height was measured at least monthly during treatment, and adrenal function assessed by overnight urinary cortisol at baseline and after 3 and 6 months of treatment. Mean regressed daily growth was significantly decreased during the treatment period in the BDP-treated group. Growth was significantly decreased in both males and females. BDP had no effect on overnight urinary cortisol production. BDP at a dose taken by many children significantly decreases statural growth in children with mild asthma, and this effect is unlikely to be mediated through the HPA (Doull IJ et al, 1995).

Out of 346 asthmatic children, 81 patients were receiving inhaled BDP. These BDP-treated patients were compared with 249 others who were on different treatments. 16 children were studied before and after starting BDP. There was a significant age difference between the BDP-treated and control groups of patients when SDS for height and weight were compared, the steroid group were significantly lower than the controls and the mean (set at zero) of the "ideal" population. The controls had a similar weight compared with the "ideal" population, but were significantly taller. Of the 16 patients studied before and after starting BDP, there was a significant negative inflection in the growth pattern, closely related to the start of BDP treatment. Furthermore, when the pre-steroid and post-steroid SDS of these patients was compared, there was a significant difference between the groups for height and weight, although the difference for weight was small. The control patients were significantly younger and thus smaller than those receiving BDP (Littlewood et al, 1988).

Plasma cortisol was measured every 20 min and sleep was monitored in 19 asthmatic children, 12 were receiving various doses of inhaled BDP. Children receiving inhaled BDP had lower cortisol secretion during the night than those who were not taking inhaled BDP, a delayed rise from the nocturnal nadir, and low early morning levels. Inhaled BDP produces a dose-dependent adrenal suppression (Law CM et al, 1986).

A study was performed to determine the effects of high doses of 2 ICs, BDP and budesonide, on biochemical indices of bone turnover (urinary hydroxyproline: creatinine and calcium: creatinine ratios, plasma alkaline phosphatase, and parathyroid hormone). During treatment with BDP there was a significant increase in the hydroxyproline: creatinine ratio (a 46% increase at 28 days), and a fall in serum alkaline phosphatase activity (a 7-4% fall at 28 days). There were no significant changes during budesonide treatment. Thus high dose inhaled BDP increased biochemical markers of bone resorption and reduced serum alkaline phosphatase, a marker of bone mineralization (Ali NJ et al, 1991).

A study reviewed potential systemic effects of ICs which included adrenal suppression, bone loss, skin thinning, increased cataract formation, decreased linear growth in children, metabolic changes, and behavioral abnormalities. Changes in adrenal function have been noted in patients using medications such as BDP and budesonide in doses exceeding 1,500 µg/day. Several short-term and cross-sectional studies have also revealed changes in biochemical markers of bone turnover and retrospective studies have found reduced bone density in asthmatics treated regularly with inhaled steroids. Although inhaled steroids shouldcontinue to be a recommended therapeutic option to all patients with symptomatic asthma, they should always be used in the lowest dosage compatible with disease control (Hanania NA et al, 1995).

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The transfer to BDP of patients who have been treated with systemic steroids for long periods of time or at high doses needs special care, since recovery from possible adrenocortical suppression may take considerable time. Reduction of the dose of systemic steroid can be commenced approximately one week after initiating treatment with BDP. The size of the reduction should correspond to the maintenance dose of systemic steroid. For patients receiving maintenance doses of 10 mg daily or less of prednisolone (or equivalent) reductions in dose of not more than 1 mg are suitable. For higher maintenance doses, larger reductions in dose may be appropriate. These oral dosage reductions should be introduced at not less than weekly intervals.

Adrenocortical function should be monitored regularly as the dose of systemic steroid is gradually reduced.

Some patients feel unwell during withdrawal of systemic steroids despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled BDP and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients weaned off oral steroids whose adrenocortical function is impaired should carry a steroid warning card indicating that they may need supplementary systemic steroids during periods of stress, eg. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and / or topical preparations, including topical steroids

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis (SmPC of Clenil Modulite inhaler, Chiesi Ltd, December 2018).

Psychiatric disorders

A multicenter, randomized, double-blind, parallel-groups study assessed the relative psychological side effects of theophylline and beclometasone in 102 asthmatic children. Patients were assigned to one of two treatments: beclometasone3 times daily or theophylline twice daily. At baseline, 1 month, and 1 year, parents completed standardized behavioral questionnaires while the children received psychometric testing of attention and concentration, memory and learning, and problem-solving. 2 significant treatment-by-period interactions were discordant, with one suggesting slightly better attention in the theophylline group, whereas the other indicated a small advantage in attention scores in the beclometasone group. Numerous significant period effects revealed that behavior and cognitive test performance improved over the 1-year period, regardless of treatment, and confirmed a well established practice effect resulting from repeated administrations of such tests. Neither theophylline nor beclometasone should be avoided out of concern for significant psychological side effects. The possibility remains that a subset of asthmatic children may be susceptible to such medication-induced changes; investigators have suggested that preschool children may be at particular risk, although no controlled studies with this age group have been conducted (Bender BG et al, 1998).

Nervous system disorders

A double-blind, double dummy, parallel-group study compared the efficacy of BDP 200 µg bid via MDI, using HFA-134a versus CFC as a propellant in 172 adult patients (86 in each group) with stable mild persistent asthma. The number of drug-related adverse reactions (adverse events with a definite, probable or possible relationship with the test treatment) was 22 in the BDP HFA group and 19 in the BDP CFC group. Episodes of headache were reported in both groups in a similar extent. No serious adverse events occurred at any time in either group. No significant changes within or between groups were reported for vital signs. (Woodcock A et al, 2002).

A total of 642 patients with chronic asthma (FEV_1 50 to 85% of predicted value and at least a predefined level of asthma symptoms) incompletely controlled with inhaled beclometasone, 200 µg twice daily using a spacer device, during the 4-week run-in period were randomly allocated, in a double-blind, double-dummy manner to 1 of 4 treatment groups: (1) montelukast 10 mg plus continuing inhaled beclometasone; (2) placebo tablet plus continuing inhaled beclometasone; (3) montelukast 10 mg and inhaled placebo (after blind beclometasone removal); and (4) placebo tablet and inhaled placebo (after blind beclometasone removal). The most commonly reported adverse experiences included headache (Laviolette M et al, 1999).

Eye disorders

Steroid usage can cause many adverse effects on the eye, the most important being steroid-induced glaucoma and cataract. Steroid-induced iatrogenic glaucoma was described for the first time in the 1950s with the observation of glaucoma following the use of systemic adrenocorticotropic hormones and topical or systemic steroids (Feroze KB et al, 2020).

A systematic review and meta-analysis was performed of case-control studies of cataracts and ICs use, which included at least 2 doses of ICs and in which the number of cases and controls using each dose of ICs was reported. The primary outcome variable was risk of cataracts. Four case-control studies were identified, with a total of 46 638 cases and 146 378 controls. There was a significant relationship between the risk of cataracts and ICs dose, with a random effects pooled odds ratio for risk of cataracts per 1000 µg increase in daily BDP dose of 1.25 (95% CI: 1.14-1.37). The risk of cataracts was increased by approximately 25% for each 1000 µg/day increase in the dose of BDP or equivalent. These findings reinforce the importance of prescribing within the therapeutic dose-response range for ICs in asthma (Weathrall AM et al, 2009).

A study investigated the relationship between ICs and the development of central serous chorioretinopathy (CSC). The medical records of three patients with CSC who were found to use inhaled adrenergic agents or corticosteroids or both were identified prospectively. 6 patients with CSC were found to be chronic users of corticosteroid (4 patients) or both beta adrenergic agonist and corticosteroid (2 patients) MDI or nasal sprays. In 3 cases, there was a close temporal correlation between the use of a corticosteroid nasal spray and the development of CSC. These findings suggest that, in patients who are susceptible, the periocular or systemic absorption of ICs may be sufficient to produce CSC in humans (Haimovici R et al, 1997).

A study determined the relationship between the clinical characteristics of patients with CSC and systemic corticosteroid therapy.17 cases were reviewed where 2 of these developed bilateral and 15 developed unilateral CSC. The duration from the beginning of corticosteroid treatment to the onset of CSC ranged from 3 days to 23 years; 9 patients developed CSC within 1 year after the beginning of the corticosteroid medication and 6 patients after more than 8 years. The amount of corticosteroid medication at the onset of CSC ranged from 5 to 1,000 mg/day equivalent prednisolone units. There was a significant correlation between age at the onset of CSC and the daily dosage of corticosteroid. These findings indicate that there is a need to monitor patients undergoing corticosteroid treatment carefully (Koyoma M et al, 2004).

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient present with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as CSCR which have been reported after use of systemic and topical corticosteroids.

Patients should be advised that this product contains small amounts of ethanol and glycerol. At the normal doses, the amounts of ethanol and glycerol are negligible and do not pose a risk to patients (SmPC of Clenil Modulite inhaler, Chiesi Ltd, December 2018).

Respiratory, Thoracic and Mediastinal Disorders

Paradoxical bronchoconstriction is the unexpected constriction of smooth muscle walls of the bronchi that occurs in the setting of an expected bronchodilatory response. This phenomenon

has been observed with β_2-agonist-containing inhaler formulations and is an under-recognized adverse event. Theories suggest that the formulation excipients can trigger airway hyperresponsiveness in patients with allergically inflamed airways. Clinicians should be aware of paradoxical bronchospasm as an adverse effect with common inhaler formulations containing β_2-agonists and counsel patients accordingly in the appropriate clinical setting (Mage JS et al, 2018).

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing, shortness of breath and cough after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. BDP should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted. Hoarseness or throat irritation may occur in some patients. These patients should be advised to rinse the mouth out with water immediately after inhalation. Use of the Volumatic™ spacer device may be considered. (SmPC of Clenil Modulite inhaler, Chiesi Ltd, December 2018).

Of 158 asthmatic patients who were placed on inhaled beclometasone, 15 (9.5%) developed either hoarseness (8), oral thrush (6), or both (1). When their adverse reactions subsided, seven of these 15 patients were rechallenged with inhaled beclometasone. These included 5 cases who developed hoarseness and three who developed Candidiasis. 1 patient had both. Oral thrush did not recur, but 60% (3/5) of patients with hoarseness had recurrence. It is concluded that patients may be restarted on inhaled beclometasone when clinically indicated; however, because of the high recurrence rate, patients who develop hoarseness should not be re-challenged. Concomitant use of oral prednisone and topical beclometasone may increase the risk of developing hoarseness or candidiasis (Settipane GA et al, 1987).

Infections and Infestations

A total of 229 children aged 6 to 15 years had throat swabs taken to determine the incidence of *Candida* colonisation of the oropharynx. 100 children (group A), who were not receiving steroids, were compared with 91 children (group B) receiving less than 500 µg of inhaled beclometasone a day and 38 children (group C) receiving 500 µg or more of inhaled beclometasone a day. Sore throat and hoarse voice were not related to the presence of candida or to treatment with inhaled steroids. The incidence of candida was greater in the groups given treatment with steroids but did not increase at a higher dosage, nor was it related to the type of inhaler used. There was only 1 case of clinical thrush in all the children studied (Shaw NJ et al, 1986).

A survey of 936 patients was performed to assess the incidence of oropharyngeal candidiasis in patients inhaling BDP in daily doses of 400 µg or less. Throat swabs from 209 (41%) patients treated with beclometasone were positive on culture for yeasts compared with positive swabs from 77 (27·2%) patients not receiving corticosteroid therapy either orally or by inhalation. Clinical oropharyngeal thrush, confirmed by culture, was detected in 28 (5·5%) patients inhaling beclometasone, 1 (0·7%) patient receiving treatment with oral prednisolone, and 2 (0·7%) patients not being treated with corticosteroids (Milne LJ et al, 1974).

The amount of *Candida* spp. was significantly greater in asthmatic patients taking inhaled steroids compared with those who were not. It was also significantly greater in patients with oral symptoms than asymptomatic patients and significantly greater in asthmatic patients treated with fluticasone than in those treated with beclometasone. Although the presence of *Candida* did not correlate with the inhaled dose of beclometasone, it did increase with the dose of fluticasone. Gargling with amphotericin B was effective in most asthmatic patients with candidiasis. Candidiasis was not due to inappropriate flow rates during inhalation of steroids (Fukushima C et al, 2003).

Candidiasis of the mouth and throat occurs in some patients, the incidence increasing with doses greater than 400 µg BDP per day. Patients with high blood levels of *Candida* precipitins, indicating a previous infection, are most likely to develop this complication. Patients may find it helpful to rinse their mouth thoroughly with water after inhalation. Symptomatic oral candidiasis can be treated with topical antifungal therapy while continuing with Clenil Modulite (SmPC of Clenil Modulite inhaler, Chiesi Ltd, December 2018).

Immune System Disorders

The purpose of this study was to investigate the occurrence of corticosteroid allergy among patients with asthma and with some complaints caused by ICs**.** Patch tests with corticosteroids were performed in 51 asthma patients with side-effects from inhalant ICs and in 50 symptom-free asthma patients. The corticosteroids and their vehicles were: betamethasone-17-valerate 1% in petrolatum, hydrocortisone-17-butyrate (Hc-17-B) 1% in ethanol, tixocortol-21-pivalate 1% in petrolatum, budesonide 0.1% in petrolatum, beclometasone dipropionate 0.1 and 0.5% in petrolatum and as inhalant powder 200 µg, and fluticasone propionate 0.1 and 0.5% in petrolatum and as inhalant powder 250 µg. 2 patients in the symptomatic group reacted to corticosteroids in patch tests, 1 to betametasone-17-valerate, Hc-17-B and budesonide, and the other to budesonide and Hc-17-B. The first patient suffered from widespread eczematous dermatitis when using beclometasone. In conclusion, delayed allergy to corticosteroids occurs occasionally in asthma, perhaps in the same frequency as in dermatitis. A positive patch test reaction usually means clinical allergy, i.e. the patient cannot use that particular steroid. Cross allergy between corticosteroids is common. However, such patients usually tolerate some other common corticosteroids (Kilpiö K et al, 2003).

Use in special Population

Pregnancy

A prospective, double-blind, double placebo-controlled randomized clinical trial of pregnant women with moderate asthma was performed. There was no significant difference in the proportion of asthma exacerbations among the 194 women in the beclometasone cohort (18.0%) versus the 191 in the theophylline cohort. The beclometasone cohort had significantly lower

incidences of discontinuing study medications caused by side effects and proportion of study visits with FEV_1 less than 80% predicted. There were no significant differences in treatment failure, compliance, or proportion of PEFR less than 80% predicted. There were no significant differences in maternal or perinatal outcomes. The treatment of moderate asthma with inhaled beclometasone versus oral theophylline resulted in similar rates of asthma exacerbations and similar obstetric and perinatal outcomes. These results favor the use of ICs for moderate asthma during pregnancy because of the improved FEV_1 and because theophylline had more side effects and requires serum monitoring (Dombrowski MP et al, 2004).

There is no experience of the use of this product in pregnancy and lactation in humans. It should not be used in pregnancy or lactation unless the expected benefits to the mother are thought to outweigh any potential risks to the fetus or neonate.

There is inadequate evidence of safety of BDP in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. There may therefore, be a risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic exposure. BDP is delivered directly to the lungs by the inhaled route and so avoids the high level of exposure that occurs when corticosteroids are given by systemic routes (SmPC of Clenil Modulite inhaler, Chiesi Ltd, December 2018).

Lactation

Although not measured, the amounts of ICs absorbed into the maternal bloodstream and excreted into breastmilk are probably too small to affect a breastfed infant. Expert opinion considers inhaled and oral corticosteroids acceptable to use during breastfeeding (Drugs and Lactation Database (LactMed).

No specific studies examining the transfer of BDP into the milk of lactating animals have been performed. It is reasonable to assume that BDP is secreted in milk, but at the dosages used for direct inhalation there is low potential for significant levels in breast milk.

There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy or lactation. However, studies of the effect of HFA-134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects (SmPC of Clenil Modulite inhaler, Chiesi Ltd, December 2018).

Effects on ability to drive and use machines

None reported

2.5.6 BENEFITS AND RISKS CONCLUSIONS

The Applicant has developed beclometasone dipropionate pressurized inhalation solution 100 µg and 200 µg. This application is being submitted under Article 10(3) (hybrid application) of European Directive 2001/83/EC (as amended) based on *in vitro* BE studies conducted with Clenil Modulite inhaler (marketed by Chiesi Limited, UK) as reference product and published scientific bibliographical evidences supporting the risk benefit profile for beclometasone dipropionate (BDP).

The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged BDP and B-17-MP, respectively. BDP is absorbed rapidly with peak plasma concentrations observed (t_{max}) at 0.3 hours. B-17-MP appears more slowly with a t_{max} of 1 hour. The tissue distribution at steady-state for BDP is moderate (20 L) but more extensive for B-17-MP (424 L). Plasma protein binding is moderately high (87%). BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). The elimination of BDP and B-17-MP are characterised by high plasma clearance (150 L/hour and 120 L/hour) with corresponding terminal elimination half-lives of 0.5 hours and 2.7 hours. The renal clearance of BDP and its metabolites is negligible.

Beclometasone dipropionate is actually a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite B-17-MP. In asthmatic patients, the inhaled drug has little immunosuppressive effect and causes minimal changes in circulating leucocytes and eosinophils. Although antigen-induced type I immediate asthmatic and nasal reactions are not inhibited by prechallenge administration of single doses of BDP, regular treatment for 1 week prior to antigen challenge inhibits such reactions in some patients. Substitution of inhaled BDP for oral maintenance corticosteroids in patients with asthma generally results in an improvement in adrenal function when the oral steroids have been administered daily.

Studies conducted over the last decade have confirmed that inhaled BDP 400 to 800 µg daily can reduce the need for oral maintenance corticosteroids in the majority of asthmatic patients requiring such therapy, and that increasing the dosage to 2000 µg daily may provide additional clinical benefit in some patients unresponsive to usual therapeutic dosages. Follow-up over a period of several years has confirmed that the initial response to inhaled beclometasone can be maintained in most patients. Recent studies indicate that BDP 400 µg daily is equally effective when administered in 2 or 4 divided doses in patients with stable asthma, but it is likely that the lower frequency of administration will be less effective when the asthma is unstable.

The most frequent side effects associated with long term use of inhaled BDP have been oropharyngeal candidiasis, hoarseness and/or sore throat. Clinical thrush has seldom become a major problem as it has usually been readily controlled with topical antifungal drugs, and has only occasionally necessitated withdrawal of therapy. The incidence of hoarseness and sore throat, like that of oropharyngeal candidiasis, has varied considerably between studies, due in

part to the different methods of eliciting side effect data. In the first few years after the introduction of inhaled BDP, there was some concern that the drug may increase the incidence of respiratory infections. However, suitably designed studies have revealed no evidence of an increase in chest infections during long term treatment.

Based on the review of the data on safety and efficacy, the benefit-risk ratio of in the treatment of is positive.

2.5.7 REFERENCES

1. Agertoft L et al (2003). Influence of particle size on lung deposition and pharmacokinetics of beclometasone dipropionate in children. Pediatr Pulmonol.;35(3):192-9
2. Ali, NJ et al (1991). Bone turnover during high dose inhaled corticosteroid treatment. Thorax, 46(3), 160–164.
3. Allen DB et al (1994). A meta-analysis of the effect of oral and inhaled corticosteroids on growth. Journal of Allergy and Clinical Immunology.;93(6):967-76.
4. Anderson PB et al (2002). Equivalent efficacy and safety of a new HFA-134a formulation of BDP compared with the conventional CFC in adult asthmatics. J Investig Allergol Clin Immunol; 12(2):107-13.
5. Ayres JG et al (1999). Acute safety of beclometasone dipropionate in a new CFC-free propellant system in asthmatic patients. Respiratory Medicine, 93(1), 27–32.
6. Bender BG et al (1998). Neuropsychological and behavioral changes in asthmatic children treated with beclometasone dipropionate versus theophylline. Pediatrics. 1998;101(3 Pt 1):355-60.
7. Blaiss MS et al (1982). Beclometasone dipropionate aerosol: hematologic and immunologic effects. Ann Allergy; 48(4):210-4.
8. Boner AL et al (1991). Effect of inhaled beclometasone dipropionate on bronchial hyperreactivity in asthmatic children during maximal allergen exposure. Pediatr Pulmonol; 10(1):2-5.
9. Bousquet J et al (2002). Clinical studies in asthmatics with a new non-extra fine HFA formulation of beclometasone dipropionate (BDP Modulite). Respir Med; 96 Suppl D: S17-27.
10. Boyd SD et al (2013). Influence of low-dose ritonavir with and without darunavir on the pharmacokinetics and pharmacodynamics of inhaled beclometasone. J Acquir Immune Defic Syndr; 63(3):355-61.
11. Brogden RN et al (1975). Beclometasone dipropionate inhaler: a review of its pharmacology, therapeutic value and adverse effects. I: Asthma. Drugs; 10(3):166-210.
12. Brogden RN et al (1984). Beclometasone dipropionate. A reappraisal of its pharmacodynamic properties and therapeutic efficacy after a decade of use in asthma and rhinitis. Drugs; 28(2):99-126.
13. Bronsky E et al (1998). Comparative clinical study of inhaled beclometasone dipropionate and triamcinolone acetonide in persistent asthma. Ann Allergy Asthma Immunol. 1998 Apr;80(4):295-302.
14. Brown, HM et al (1972). Beclometasone Dipropionate: A New Steroid Aerosol for the Treatment of Allergic Asthma. BMJ, 1(5800), 585–590.
15. Champion P et al (1975). Beclometasone dipropionate in asthma. Can Med Assoc J. 1975 Aug 9;113(3):213-8.

16. Dahl R et al (1997). Equivalence of asthma control with new CFC-free formulation HFA-134a beclometasone dipropionate and CFC-beclometasone dipropionate. Br J Clin Pract; 51(1):11-5.
17. Daley-Yates PT et al (2001). Beclometasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. Br J Clin Pharmacol; 51(5):400-9.
18. DeCotiis et al (1981). The Effect of Inhaled Beclometasone on Serum Immunoglobulins. Allergy and Asthma Proceedings, 2(3), 153–156.
19. Dombrowski MP et al (2004). Randomized trial of inhaled beclometasone dipropionate versus theophylline for moderate asthma during pregnancy. American journal of obstetrics and gynecology, 190(3), 737–744.
20. Doull IJ et al (1995). Growth of prepubertal children with mild asthma treated with inhaled beclometasone dipropionate. American Journal of Respiratory and Critical Care Medicine, 151(6), 1715–1719
21. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Beclometasone. [Updated 2020 Apr 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501105/
22. Feroze KB et al (2020). Steroid Induced Glaucoma. [Updated 2020 Jul 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430903/
23. Fukushima C et al (2003). Oral candidiasis associated with inhaled corticosteroid use: comparison of fluticasone and beclometasone. Ann Allergy Asthma Immunol ;90(6):646-51
24. Grzelewska-Rzymowska I et al (2003). Comparison of the efficacy and safety of high doses of beclometasone dipropionate suspension for nebulization and beclometasone dipropionate via a metered-dose inhaler in steroid-dependent adults with moderate to severe asthma. Respir Med ;97 Suppl B: S21-6.
25. Gupta D et al (2000). Hypothalamo-pituitary-adrenal axis function in asthmatics taking low dose inhaled beclometasone dipropionate. J Assoc Physicians India ;48(7):682-4
26. Haimovici R et al (1997). Central serous chorioretinopathy associated with inhaled or intranasal corticosteroids. Ophthalmology; 104(10):1653-60.
27. Hanania NA et al (1995). Adverse effects of inhaled corticosteroids. Am J Med. 1995 Feb;98(2):196-208
28. Harrison LI et al (1997). Pharmacokinetics and dose proportionality of beclometasone from three strengths of a CFC-free beclometasone dipropionate metered-dose inhaler. Biopharm Drug Dispos ;18(7):635-43
29. Harrison LI et al (1999). Adrenal effects and pharmacokinetics of CFC-free beclometasone dipropionate: a 14-day dose-response study. J Pharm Pharmacol ;51(3):263-9.
30. Harrison LI et al (1999). Pharmacokinetic differences between chlorofluorocarbon and chlorofluorocarbon-free metered dose inhalers of beclometasone dipropionate in adult asthmatics. J Pharm Pharmacol; 51(11):1235-40.

31. Harvey LL et al (1976). Beclometasone dipropionate aerosol in the treatment of steroid-dependent asthma. A 12-week double-blind study comparing beclometasone dipropionate and a vehicle aerosol. Chest ;70(03):345-50.
32. Hasan AA et al (2020). Effects of montelukast versus inhaled beclometasone on asthma control and Immunoglobulin-E levels in asthmatic children. Matrix Sci Med 2020; 4:112-5
33. Israel E et al (2002). Effects of montelukast and beclometasone on airway function and asthma control. J Allergy Clin Immunol; 110(6):847-54.
34. Jenkins CR et al (1988). Effect of prednisone and beclometasone dipropionate on airway responsiveness in asthma: a comparative study. Thorax ;43(5):378-84.
35. Juniper EF et al (1999). Health-related quality of life in moderate asthma: 400 microg hydrofluoroalkane beclometasone dipropionate vs 800 microg chlorofluorocarbon beclometasone dipropionate. The Study Group ;116(5):1297-303
36. Kass I et al (1977). Beclometasone dipropionate aerosol in the treatment of steroid-dependent asthmatic patients. An assessment of 18 months of therapy ;71(6):703-7
37. Kerigan AT et al (1977). Subsittution of inhaled beclometasone dipropionate for ingested prednisone in steroid-dependent asthmatics. Can Med Assoc;116(8):867-71.
38. Kershnar H et al (1978). Treatment of chronic childhood asthma with beclometasone dipropionate aerosols: II. Effect on pituitary-adrenal function after substitution for oral corticosteroids. Pediatrics ;62(2):189-97.
39. Kilpiö K et al (2003). Corticosteroid allergy in asthma. Allergy; 58(11):1131-5.
40. Klein R et al (1977). Treatment of chronic childhood asthma with beclometasone dipropionate aerosol: I. A double-blind crossover trial in nonsteroid-dependent patients. Pediatrics ;60(1):7-13.
41. Koyama M et al (2004). Seventeen cases of central serous chorioretinopathy associated with systemic corticosteroid therapy. Ophthalmologica; 218(2):107-10.
42. Laurikainen K et al (1994). Comparison of two beclometasone dipropionate inhalation aerosol spacer combinations in the treatment of asthma. Int J Clin Pharmacol Ther ;32(6):293-8.
43. Laviolette M et al (1999). Montelukast Added to Inhaled Beclometasone in Treatment of Asthma. American Journal of Respiratory and
44. Law CM et al (1986). Nocturnal adrenal suppression in asthmatic children taking inhaled beclometasone dipropionate. The Lancet, 327(8487), 942–944.
45. Leach CL et al (1998). Improved airway targeting with the CFC-free HFA-beclometasone metered-dose inhaler compared with CFC-beclometasone. Eur Respir J ;12(6):1346-53.
46. Leach CL et al (2002). Lung deposition of hydrofluoroalkane-134a beclometasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclometasone: a cross-over study in healthy volunteers. Chest;122(2):510-6.
47. Lee TL et al. Assessment of efficacy and systemic safety of a new CFC-free formulation of inhaled BDP in asthmatic children. Pediatr Asthma Allergy lmmunol
48. Lipworth BJ et al (1999). Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med;159(9):941-55.

49. Littlewood J et al (1988). Growth retardation in asthmatic children treated with inhaled beclometasone dipropionate. The lancet, 331(8577), 115–116.
50. Magee JS et al (2018). Paradoxical Bronchoconstriction with Short-Acting Beta Agonist. Am J Case Rep; 19:1204-1207.
51. Malmstrom K et al (1999). Oral Montelukast, Inhaled Beclometasone, and Placebo for Chronic Asthma. Annals of Internal Medicine, 130(6), 487.
52. McAllen MK et al (1974). Steroidaerosols in asthma: an assessment of betamethasone valerate and a 12-month study of patients on maintenance treatment. Br Med; 1(5900):171-5.
53. Mellis CM et al (1976). Beclometasone dipropionate aerosol for asthmatic children requiring maintenance oral steroid therapy. Med J Aust ;1(25):957-62.
54. Milanowski J et al (1999). Inhaled beclometasone (BDP) with non-CFC propellant (HFA 134a) is equivalent to BDP-CFC for the treatment of asthma. Respir Med ;93(4):245-51
55. Milne LJ et al (1974). Beclometasone dipropionate and oropharyngeal candidiasis. Br Med J ;3(5934):797-8.
56. Molema J et al (1988). Effects of inhaled beclometasone dipropionate on beta 2-receptor function in the airways and adrenal responsiveness in bronchial asthma. Eur J Clin Pharmacol; 34(6):577-83.
57. Pruteanu AI et al (2014). Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. Cochrane Database Syst Rev ;(7):CD009878.
58. Rao R et al (1999). Systemic effects of inhaled corticosteroids on growth and bone turnover in childhood asthma: a comparison of fluticasone with beclometasone. Eur Respir J; 13(1):87-94.
59. Ryan G et al (1985). Effect of beclometasone dipropionate on bronchial responsiveness to histamine in controlled nonsteroid-dependent asthma. J allergy clin immunol; 75(1 pt 1):25-30.
60. Settipane GA et al (1987). Rechallenge of patients who developed oral candidiasis or hoarseness with beclometasone dipropionate. N Engl Reg Allergy Proc; 8(2):95-7.
61. Shaw NJ et al (1986). Inhaled beclometasone and oral candidiasis. Arch Dis Child; 61(8):788-90.
62. Simons FER et al (1997). A Comparison of Beclometasone, Salmeterol, and Placebo in Children with Asthma. New England Journal of Medicine, 337(23), 1659–1665.
63. Smith JM et al (1973). A clinical trial of beclometasone dipropionate aerosol in children and adolescents with asthma. Clinical & Experimental Allergy, 3(3), pp.249-253.
64. Soria I et al (1998). Beclometasone relative availability of oral versus inhaled beclometasone dipropionate from an HFA-134A metered dose inhaler. Biopharm Drug Dispos ;19(5):297-302.
65. Summary of product characteristics of Clenil Modulite inhaler, Chiesi Ltd, December 2018

66. Tinkelman DG et al (1993). Aerosol beclometasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. Pediatrics ;92(1):64-77.
67. Trescoli C et al (1998). Systemic activity of inhaled and swallowed beclometasone dipropionate and the effect of different inhaler devices. Postgrad Med J; 74(877):675-7.
68. Verberne AA et al (1997). One Year Treatment with Salmeterol Compared with Beclometasone in Children with Asthma. American Journal of Respiratory and Critical Care Medicine, 156(3), 688–695.
69. Vogt F et al (1976). Beclometasone dipropionate aerosol in the treatment of chronic bronchial asthma. Journal of Allergy and Clinical Immunology, 58(2), 316–321.
70. Vondra V et al (2002). A new HFA-134a propellant in the administration of inhaled BDP via the Jet spacer: controlled clinical trial vs the conventional CFC. Respir Med ;96(10):784-9
71. Weatherall M et al (2009). Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis. Respirology; 14(7):983-90.
72. Webb DR et al (1998). Efficacy of inhaled beclometasone dipropionate and budesonide in the treatment of asthma. Respir Med; 92 Suppl B: 7-14.
73. Woodcock A et al (2002). Effects on lung function, symptoms, and bronchial hyperreactivity of low-dose inhaled beclometasone dipropionate given with HFA-134a or CFC propellant. J Aerosol Med ;15(4):407-14.
74. Woodcock A et al (2002). Modulite technology: pharmacodynamic and pharmacokinetic implications. Respir Med ;96 Suppl D: S9-15
75. Wyatt R et al (1978). Effects of inhaled beclometasone dipropionate and alternate-day prednisone on pituitary-adrenal function in children with chronic asthma. N Engl J Med ;299(25):1387-92.
76. Berkowitz R et al (1998). A comparison of triamcinolone acetonide MDI with a built-in tube extender and beclometasone dipropionate MDI in adult asthmatics. Chest;114(3):757-65.
77. Nathan RA et al (1997). A comparison of double-strength beclometasone dipropionate (84 microg) MDI with beclometasone dipropionate (42 microg) MDI in the treatment of asthma. Chest. Jul;112(1):34-9.
78. Toogood JH et al (1977). A graded dose assessment of the efficacy of beclometasone dipropionate aerosol for severe chronic asthma. J Allergy Clin Immunol. ;59(4):298-308.
79. Singh A et al (2016). Comparison of clinical effects of beclometasone dipropionate & budesonide in treatment of children with mild persistent asthma: A double-blind, randomized, controlled study. Indian J Med Res ;144(2):250-257.
80. Vandewalker M et al (2017). Efficacy and safety of beclometasone dipropionate breath-actuated or metered-dose inhaler in pediatric patients with asthma. Allergy Asthma Proc;38(5):354-364.
81. Kerrebijn KF. Beclometasone dipropionate in long-term treatment of asthma in children. J Pediatr. 1976 Nov;89(5):821-6.
82. Petersen R et al (2004). Treatment of exercise-induced asthma with beclometasone dipropionate in children with asthma. Eur Respir J ;24(6):932-7.
83. Svendsen UG et al (1992). High-dose inhaled steroids in the management of asthma. A comparison of the effects of budesonide and beclometasone dipropionate on pulmonary

function, symptoms, bronchial responsiveness and the adrenal function. Allergy. 1992 Apr;47(2 Pt 2):174-180.

84. Parakh U et al (2004). A comparative evaluation of the efficacy of inhaled beclometasone dipropionate Budesonide and fluticasone propionate in the management of bronchila asthma. Indian J Allergy Asthma Immunol.18(1)33-38.
85. Nathan RA egt al (1999). A six-month, placebo-controlled comparison of the safety and efficacy of salmeterol or beclometasone for persistent asthma. Ann Allergy Asthma Immunol. 1999 Jun;82(6):521-9.
86. Boe J et al (1989). Comparison of dose-response effects of inhaled beclometasone dipropionate and budesonide in the management of asthma. Allergy. 1989 Jul;44(5):349-55
87. Pauwels RA et al (1998). Safety and efficacy of fluticasone and beclometasone in moderate to severe asthma. Belgian Multicenter Study Group. Am J Respir Crit Care Med. 1998 Mar;157(3 Pt 1):827-32.
88. Williams B et al (2001). Long-term asthma control with oral montelukast and inhaled beclometasone for adults and children 6 years and older. Clin Exp Allergy. 2001 Jun ;31(6):845-54.
89. Tarlo SM et al (1988). Six-Month Double-Blind, Controlled Trial of High Dose, Concentrated Beclometasone Dipropionate in the Treatment of Severe Chronic Asthma. Chest, 93(5), 998–1002. doi:10.1378/chest.93.5.998