

Clenil Modulite, a CFC-free MDI with no adjustment on switching

Steve Chaplin MSc, MRPharmS and Steve Head FRCGP

PRODUCT PROFILE

Proprietary name: Clenil Modulite

Constituent: beclometasone dipropionate

Indication: prophylactic management of mild, moderate, or severe asthma in adults or children

Dosage and method of administration: for inhalation use only, the aerosol spray is inhaled through the mouth, synchronising aerosol actuation with inspiration of breath; a spacer device may be used by patients who have difficulty; starting dose according to severity of the disease, adjusted until control is achieved, then titrated to the lowest dose at which effective control of asthma is maintained; *adults (including the elderly)* 50µg, 100µg, 200µg: starting dose 200µg twice daily, increased to 600-800µg daily in severe cases; 250µg: usually 1000µg daily, increased to 2000µg daily if necessary, reduced when asthma has stabilised; total daily dosage should be administered as two to four divided doses; *children* 50µg, 100µg: starting dose 100µg twice daily, may be increased up to 400µg, administered in two to four divided doses; all patients 15 years of age and under must use a Volumatic spacer; 200µg, 250µg: not recommended

Contraindications: hypersensitivity to any of the components

Precautions: patients should be properly instructed on the use of the inhaler; prolonged treatment with high doses of inhaled corticosteroids may result in systemic effects including growth retardation and clinically significant adrenal suppression: it is recommended that the height and adrenocortical function of children receiving prolonged treatment are monitored regularly; 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; as with all inhaled corticosteroids special care is necessary in patients with active or quiescent pulmonary tuberculosis; patients should be advised that this product contains small amounts of ethanol (approximately 9mg per actuation) and glycerol and do not pose a risk to patients; as with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing – this should be treated immediately with a fast-acting inhaled bronchodilator

Pregnancy and lactation: not recommended during pregnancy or breastfeeding

Interactions: Clenil Modulite contains a small amount of ethanol – there is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole

Side-effects: systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods: these may include decrease in bone mineral density, cataract and glaucoma; hypersensitivity reactions including rashes, urticaria, pruritus and erythema, and oedema of the eyes, face, lips and throat, have been reported; candidosis of the mouth and throat occurs in some patients, the incidence increasing with doses greater than 400µg per day; hoarseness or throat irritation may occur in some patients

Presentation/cost: CFC-free MDI, 200 doses: 50µg per dose, £3.85; 100µg per dose, £7.72; 200µg per dose, £16.83; 250µg per dose, £16.95



Clenil Modulite is the first CFC-free metered-dose inhaler directly interchangeable with existing CFC-containing inhalers. In our New products review, Steve Chaplin presents the clinical data relating to its bioequivalence and Dr Steve Head comments on its place in treatment.

As long ago as 1998, the NHS announced the process by which it would fulfil its Montreal Protocol obligations to replace ozone-damaging chlorofluorocarbons (CFCs) with safer hydrofluoralkanes (HFAs).¹ Most CFCs had been phased out by 1996 but medical devices using these propellants were allowed a deferral.

Few expected the process of replacing CFC-containing beclometasone inhalers to take so long and, as time passes, an increasing scarcity of CFCs is adding a new urgency to complete the long-awaited switch to ozone-friendly devices.

The problem is, there has only been one CFC-free beclometasone inhaler and two is the minimum needed to start the process of withdrawing licences for CFC products.

Plans have gone smoothly for bronchodilators, leading to a

Total daily dose (µg per day)				
CFC-BDP	200-250	300	400-500	600-750
Clenil Modulite	200-250	300	400-500	600-750
Qvar	100	150	200	300
Total daily dose (µg per day)				
CFC-BDP	800-1000	1100	1200-1500	1600-2000
Clenil Modulite	800-1000	1100	1200-1500	1600-2000
Qvar	400	500	600	800

Table 1. Conversion table for dosing with CFC-containing beclometasone dipropionate (CFC-BDP) and the CFC-free inhalers Clenil Modulite and Qvar

number of different brands that are essentially equivalent. The same has not been true for inhaled beclometasone.

Qvar, the first CFC-free beclometasone metered-dose inhaler (MDI), is 2-2.5 times more potent than the CFC-containing alternatives because it generates an aerosol of smaller particles, achieving greater penetration and lung deposition than the CFC-MDIs.

This lack of bioequivalence between new and old beclometasone MDIs means that patients switching to Qvar must start at around half their previous dose (see Table 1), expressed as beclometasone equivalents, *ie* Qvar 100µg rather than 200-250µg beclometasone or budesonide from a CFC-MDI or 100µg fluticasone (Flixotide) for well-controlled patients. The patient should then be reassessed to determine whether dose adjustment is needed.

Clenil Modulite is the first CFC-free beclometasone MDI that is claimed to be bioequivalent with CFC-containing formulations, meaning that patients can be switched from their old device dose-for-dose. It is licensed for the prophylaxis of mild, moderate or severe asthma in adults or children

(note that Qvar is not licensed for use in children).

The technology

The nature of the aerosol generated by an MDI depends on the design of the device and the properties of the propellant and the drug.

Lung penetration is determined by the size of the drug particles in the aerosol: only particles with a median diameter of 1-5µm reach the airways, with those at the upper end of the range deposited in large airways and those at the lower end deposited peripherally. The effectiveness of the device also depends on the patient's ability to co-ordinate actuation and inhalation.

In CFC-MDIs, a suspension of beclometasone is forced through an orifice to generate a fast-moving aerosol comprising relatively large particles (median diameter 3.4µm).² Qvar is formulated as a solution and generates an aerosol with smaller particle size (median 1.1µm),² achieving greater lung penetration.

The characteristics of the Modulite device have been designed to deliver an aerosol with properties that more closely resemble those of a CFC-MDI; in particular, glycerol is added to the beclometasone solution to modify

the particle size.² The median particle size in the aerosol generated by Clenil Modulite is 2.9µm and the distribution of particle sizes more closely matches that of CFC-containing MDIs than Qvar (Figure 1).² The aerosol from the Modulite device is also slower moving and lasts longer; this, says manufacturer Trinity-Chiesi, might make it easier for patients to get the co-ordination right.³

Clinical trials

Three randomised double-blind trials have investigated the equivalence of Clenil Modulite with CFC beclometasone in adults^{4,5} and children.⁶

A total of 116 adults with mild to moderate asthma, with a forced expiratory volume in one second (FEV₁) ≥60 per cent, were randomised to treatment with Clenil Modulite or Becotide (500µg twice daily) for 12 weeks.⁴ Morning and evening peak flow rates did not change during treatment and there were no significant differences between the two groups at any time. There were also no significant differences in secondary endpoints such as performance in lung function tests, consumption of salbutamol or clinical symptoms.

Similar findings were reported in 172 adults with mild asthma (FEV₁ >90 per cent) treated for six weeks at a dosage of 200µg twice daily.⁵ Asthma control tended to improve in all groups in both studies.

In 218 children with mild to moderate asthma (FEV₁ 60-90 per cent), beclometasone 400µg twice daily was administered via a Clenil Modulite 50 or 100µg inhaler or Becotide 50.⁶ At fortnightly assessments over 12 weeks, there were no significant differences between the groups in morning or evening peak flow rates.

Lung function tests and asthma control improved in all patients during the study, though both Clenil Modulite inhalers were associated with significantly greater improvements in FEV₁ and forced vital capacity (FVC) compared with Becotide; these findings could be explained by differences between the groups at baseline or concurrent salbutamol use.

No published study has reported patients' experiences of using Clenil Modulite; the claim that this device may be easier to co-ordinate is therefore unsupported. Compliance rates in the three trials were 93-98 per cent, with no differences between the inhalers.

The Medicines and Healthcare products Regulatory Agency (MHRA) has advised prescribers to specify the brand when prescribing a CFC-free beclometasone MDI.⁷

Adverse effects

There were no differences between Clenil Modulite and Becotide inhalers in the frequency or nature

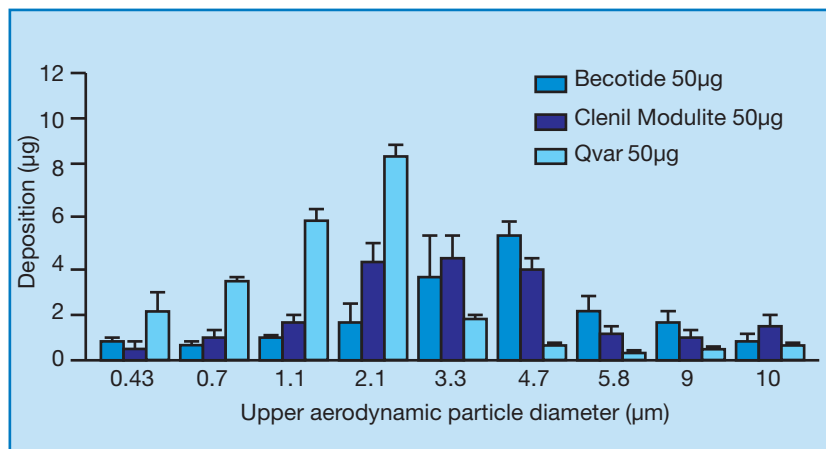


Figure 1. *In-vitro* distribution of aerosol particle size with Becotide, Clenil Modulite and Qvar²

of adverse effects. Morning serum cortisol levels in adults⁴ and children⁶ were not significantly different. Several patients noted the different taste of the CFC-free device.

Summary

Clenil Modulite is a CFC-free beclometasone MDI that is bioequivalent with CFC-MDIs but not, therefore, with Qvar, the only other CFC-free MDI currently available.

Clinical trials have consistently shown no differences in lung function, asthma control or tolerability between Clenil Modulite and Becotide, and patients may be switched to the new device without a change in dose.

Possible improvements in co-ordinating actuation and inhalation with Clenil Modulite have not been demonstrated.

By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

Steve Head FRCP

The lack of a simple range of interchangeable CFC-free beclometasone inhalers is disappointing and has led to the potential for confusion and prescribing errors. The introduction of Clenil Modulite is therefore welcome, though other bioequivalent choices will probably need to be available before the withdrawal of the CFC-containing inhalers is considered.

The reported studies showing bioequivalence between CFC-containing MDIs and the new inhaler are encouraging. The

doses used in the studies are at the higher end of current practice but we can hopefully assume bioequivalence at lower doses.

The only other CFC-free inhaler available has twice the bioavailability of the CFC-based beclometasones and can be a source of confusion. Dose adjustments need to be made not only when starting with the MDI but, more importantly, when stepping up to, say, a beta₂-agonist/steroid compound preparation, *ie* Seretide or Symbicort. It is the latter that is especially concerning because of the dangers of inadvertently reducing the effective dose of steroid in a patient whose asthma is deteriorating.

Some environmentally conscious prescribers may have moved on to Qvar or alternative dry-powder inhalers to avoid CFC-containing inhalers but CFC MDIs remain the most widely prescribed beclometasone inhaler.

While it is unlikely that CFC-containing inhalers will be withdrawn in the near future, it is more likely that CFCs will become increasingly hard to source and this may lead to supply problems. Switching patients to Clenil Modulite should be easy, although patients should be warned about a slight change in taste. It will, of course, increase prescribing costs.

For the foreseeable future it is recommended that CFC-free

inhalers are prescribed by brand name: writing beclometasone MDI (CFC free) will not make it clear to the pharmacist which product you require.

By Dr Head, a general practitioner in New Ollerton, Nottinghamshire

References

1. Department of Health. Phase out of CFC containing metered dose inhalers for the treatment of asthma and COPD. Health Service Circular HSC 1998/180 (www.dh.gov.uk/assetRoot/04/01/18/72/04011872.pdf; accessed 22.1.07).
2. Ganderton D, Lewis D, Davies R, *et al*. Modulite: a means of designing the aerosol generated by pressurized metered dose inhalers. *Resp Med* 2002;96(suppl.D):S3-S8.
3. Trinity-Chiesi Pharmaceuticals Ltd. A medicines management review of Clenil Modulite. February 2006.
4. Anderson PB, Langley SJ, Mooney P, *et al*. Equivalent efficacy and safety of a new HFA-134a formulation of BDP compared with the conventional CFC in adult asthmatics. *J Invest Allergol Clin Immunol* 2002;12:107-13.
5. Woodcock A, Williams A, Batty L, *et al*. Effects on lung function, symptoms and bronchial hyper-reactivity of low-dose inhaled beclometasone dipropionate given with HFA-134a or CFC propellant. *J Aerosol Med* 2002;15:407-14.
6. Lee TL, Adler L, McLaren G, *et al*. Assessment of efficacy and systemic safety of a new chlorofluorocarbon-free formulation of inhaled beclometasone dipropionate in asthmatic children. *Pediatr Asthma Allergy Immunol* 2002;15:133-43.
7. Woods K. Beclometasone dipropionate pressurised metered dose inhaler. Medicines and Healthcare products Regulatory Agency. 8 August 2006 (www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024433&RevisionSelectionMethod=LatestReleased; accessed 17.3.07).