Core Safety Profile

Active substance: Clenbuterol
Pharmaceutical form(s)/strength: Tablets 10 and 20 mcg
Syrup 5 mcg/5ml (for children) and 10 mcg/5ml
Solution for inhalation and oral use 59 mcg/ml
P RMS: AT/H/PSUR/0003/002
Date of FAR: 27.04.2011
4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The individual dosage of clenbuterol should be determined by the physician before commencement of treatment. Patients should also be kept under medical observation during treatment (e.g. by regular peak-flow measurements).

Unless otherwise prescribed, the recommended total daily dose for adults and children over 12 years of age is 40 mcg/day, given in 2 single applications of 20 mcg of clenbuterol each in intervals of 12 hours.

In severe bronchospasm, treatment may be initiated with dosages up to 80 mcg/day; as therapy continues, this dose can often be reduced to 20 mcg/day (10 mcg twice daily).

The recommended total daily dose for children is 1.2 mcg per kg bodyweight, ranging from 0.8 mcg to 1.5 mcg per kg bodyweight clenbuterol.

Because there is limited information in children under the age of 6, the recommended dosages for this age group are to be given under medical supervision only.

**Tablets 20 mcg**

- Adults and children over 12 years: 20 mcg (one tablet) twice daily
- Children under 12 years: according to bodyweight (see below)

**Syrup 10 mcg/5 ml**

- Adults and children over 12 years: 10 ml (20 mcg) 2-3 times daily
- Children 6 - 12 years: 5 ml (10 mcg) 3 times daily

**Syrup 5 mcg/5 ml for children and infants**

- Children 6-12 years (22 - 35 kg): 15 ml (15 mcg) twice daily
- Children 4-6 years (16 - 22 kg): 10 ml (10 mcg) twice daily
- Children 2-4 years (12 - 16 kg): 7.5 ml (7.5 mcg) twice daily
- Infants 8-24 months (8 - 12 kg): 5 ml (5 mcg) twice daily
- Infants up to 8 months (4 - 8 kg): 2.5 ml (2.5 mcg) twice daily

**Solution (7 drops ~ 20 mcg) for oral and inhalative use**

**Oral**

- Adults and children over 12 years: 7 drops (~ 20 mcg) twice daily
- Children under 12 years: according to bodyweight (see above)

**Inhalation**

- Adults and children over 12 years: 4 - 7 drops (~10 to 20 mcg) per inhalation 2 - 3 times daily
• Children 6-12 years: 4 drops (~10 mcg) per inhalation 2 - 3 times daily

After appropriate dilution with e.g. 3-5 ml physiological saline, clenbuterol solution may be used for inhalation with a nebulizer or respirator. Prior to application, the inhalation solution should be warmed-up to body temperature.

Inhalation should last 5-10 minutes.

4.3 CONTRAINDICATIONS

• Hypertrophic obstructive cardiomyopathy, tachyarrhythmia.

• Hypersensitivity to clenbuterol or any excipient of the product.

• In case of rare hereditary conditions that may be incompatible with an excipient of the product the use of the product is contraindicated (see section 4.4).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Other sympathomimetic bronchodilators should only be used concomitantly with clenbuterol under strict medical supervision. Anticholinergic bronchodilators, however, may be inhaled at the same time.

Oral forms of clenbuterol are not suitable for the symptom-oriented treatment of acute asthma attacks.

In the following conditions, clenbuterol should only be used after careful risk-benefit assessment:

Insufficiently controlled diabetes mellitus, recent myocardial infarction, severe organic heart or vascular disorders, pheochromocytoma, hyperthyroidism.

Cardiovascular effects may be seen with sympathicomimetic drugs, including clenbuterol, whose frequency and severity are dose-dependent. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta-agonists. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving clenbuterol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

In case of acute, rapidly worsening dyspnea (difficulty in breathing), a physician should be consulted immediately.

In case of prolonged use the patient should be reevaluated for the addition or the increase of anti-inflammatory therapy (e.g. inhaled corticosteroids) to control airway inflammation and to prevent long-term damage.

If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of beta-agonists such as clenbuterol beyond the recommended dose over extended periods of time. The use of increasing amounts of beta-agonists on a regular basis to control symptoms of bronchial obstruction may suggest declining disease control. In this situation, the patient's therapy plan, and in particular the adequacy of anti-inflammatory
therapy, should be reviewed to prevent potentially life threatening deterioration of disease control.

Potentially serious hypokalaemia may result from beta-2-agonist therapy. Particular caution is advised in severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives (theophylline), corticosteroids, and diuretics. Hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. In such situations, monitoring of serum potassium levels is recommended.

**Tablets 20 mcg**

One tablet contains 109.98 mg lactose resulting in 440 mg of lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

**Syrup 10 mcg/5 ml**

5 ml syrup contain 1.4 g of sorbitol resulting in 22.4 g of sorbitol per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine. It may also have a mild laxative effect.

**Syrup 5 mcg/5 ml for children and infants**

5 ml syrup contain 1.4 g of sorbitol resulting in 22.4 g of sorbitol per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine. It may also have a mild laxative effect.

**Solution (7 drops ~ 20 mcg) for oral and inhalative use**

Clenbuterol solution for inhalation contains the (antimicrobial) preservative benzalkonium chloride and the stabiliser disodium edetate. It has been shown that these components may cause bronchoconstriction in some patients.

**Benzalkonium chloride:**

Clenbuterol solution for inhalation contains the preservative benzalkonium chloride. When inhaled this preservative may cause bronchospasm in sensitive patients with hyper reactive airways.

The use of clenbuterol leads to positive results in tests for nonclinical substance abuse, e.g. athletic performance enhancement.

For additional risks associated with overdose of clenbuterol, see section 4.9.

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Beta-adrenergics, anticholinergics, xanthine derivatives (theophylline) and corticosteroids may enhance the effect of clenbuterol. The concomitant administration of other beta-mimetics, systemically absorbed anticholinergics and xanthine derivatives (theophylline) may increase the side effects.
Beta-receptor blockers counteract the action of clenbuterol.

Beta-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta adrenergic agonists may be enhanced.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may sensitize the myocardium to the arrhythmogenic effects of beta-agonists.

4.6. FERTILITY, PREGNANCY AND LACTATION

There is limited data from the use of clenbuterol in pregnant women. The inhibitory effect of clenbuterol on uterine contraction should be taken into account particularly prior to labour. With respect to reproductive toxicity animal studies did not indicate direct or indirect harmful effects unless the Maximum Recommended Human Daily Dose was exceeded by about a 1000-fold.
Pre-clinical studies have shown that clenbuterol is excreted into breast milk; should clenbuterol therapy be indicated, the infant should be weaned.
No studies on the effect on human fertility have been conducted. Animal studies did not indicate direct or indirect harmful effects with respect to fertility.
As a precautionary measure, it is preferable to avoid the use of clenbuterol during pregnancy and lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness during treatment with clenbuterol. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

General Description

In analogy to other betamimetics, clenbuterol may cause the below mentioned betamimetic side effects including serious hypokalaemia. Like in all inhalation therapy clenbuterol may show symptoms of local irritation.

Table of Adverse Reactions

Adverse reactions have been ranked under headings of frequency using the following convention:

Very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1.000 to < 1/100); rare (> 1/10.000 to < 1/1.000); very rare (< 1/10.000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Immune system disorders:
Uncommon: Hypersensitivity

Metabolism and nutrition disorders:
Not known: Hypokalaemia

Psychiatric disorders:
- Common: Restlessness
- Uncommon: Nervousness

Nervous system disorders:
- Common: Headache
- Common: Tremor
- Uncommon: Dizziness

Cardiac disorders:
- Common: Palpitations
- Uncommon: Arrhythmias
- Uncommon: Tachycardia
- Not known: Myocardial ischaemia

Respiratory, thoracic and mediastinal disorders (only applicable to solution for inhalative use):
- Uncommon: Bronchospasm paradoxical
- Uncommon: Throat irritation
- Rare: Cough

Gastrointestinal disorders:
Common: Nausea

Musculoskeletal, connective tissue and bone disorders:
- Uncommon: Muscle spasm
- Uncommon: Myalgia

Special Populations
In diabetic patients, increased blood glucose levels have been observed.
4.9 OVERDOSE

Symptoms

The expected symptoms with overdosage are those of excessive beta-stimulation, i.e. any of the symptoms listed under side effects, hyperglycaemia, hypertension, hypotension, widening of pulse pressure, anginal pain and arrhythmia. Life threatening and fatal outcomes have been observed particularly when clenbuterol overdoses were associated with illicit drug use.

Therapy

Treatment consists of discontinuation of clenbuterol together with appropriate symptomatic therapy. Administration of sedatives, tranquillizers, in severe cases intensive therapy. Non-selective beta-receptor blockers, such as propranolol, are suitable as specific antidots. However, a possible increase in bronchial obstruction must be taken into account, and the dose of the beta-blocker should be adjusted carefully in patients suffering from bronchial asthma.

Treatment of overdosage by antidots should be cumulative at short intervals, depending on symptoms. It should be noted that the action of clenbuterol may outlast that of the antidot; therefore, it may be necessary to repeat the administration of the beta-blocker.