



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

4 February 2020

Information Management Division

**Template for preliminary data analysis plan**

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**Background**

Background	Clenbuterol is a beta-2-agonist used in the treatment of asthma. Clenbuterol is nationally authorised in six Member States in the EU, including Germany. There is known illicit use of clenbuterol, including countries where clenbuterol is not authorised. Clenbuterol can be used to build muscle, burn fat and improve sports performance.
Description of research question	The question is if there is evidence that clenbuterol is selectively prescribed for purposes of muscle building, weight management or sports or to patients at risk of abuse in comparison to other selective beta-2-agonists.

**Outline of proposed data analysis**

- 2000 to June 2019
- IMRD-Germany (IMS Disease Analyzer Germany)
- Specialities that account for >95% of all clenbuterol prescribing will be included in the study
- Definition of study population:
  - No restriction with regard to age or gender.
  - No restriction with regard to disease or indication.

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- Patients with a concomitant first prescription for both clenbuterol and another selective beta-2-agonist on the same date will be excluded.
  - Patients will be required to have a minimum observation time of 180 days prior to their first prescription for a selective beta-2-agonist for the assessment of baseline factors.
  - The study will focus on baseline risk factors and indications for use at first start of treatment.
- Definition of exposure:
- Clenbuterol will be identified by searching for 'clenbuterol' in the substance name. Products containing plain clenbuterol are classified as EphMRA ATC code 'R03A' (beta-2-agonists). Products containing clenbuterol in combination with ambroxol are classified as EphMRA ATC code 'R05C' (expectorants). Other selective beta-2-agonists will be identified by searching for the EphMRA ATC code 'R03A', excluding products containing clenbuterol. In addition, the EphMRA ATC code 'R05C' will be used to identify cough products containing other selective beta-2-agonists besides clenbuterol (i.e. terbutaline and fenoterol).
  - Age, gender and respiratory diagnoses on the first prescription date for a selective beta-2-agonist will be analysed.
  - The entire history of the patient up to the first prescription date for a selective beta-2-agonist will be analysed to identify patients possibly prescribed clenbuterol for muscle building, weight management or sports, and to identify patients at increased risk of abuse.
- Definition of medical events
- The following conditions will be identified through ICD 10 codes, in some cases supplemented by searching for specific text strings in the medical event texts (diagnosis free text fields):
    - Respiratory diagnoses:
      - Chronic lower respiratory disease: ICD 10 codes J40 to J47.
      - Other respiratory disease: ICD 10 codes J00-J39 (acute upper respiratory infections, influenza and pneumonia, other acute lower respiratory infections, other diseases of upper respiratory tract) or J60 – J99 (lung diseases due to external agents, other respiratory diseases principally affecting the interstitium, suppurative and necrotic conditions of lower respiratory tract, other diseases of pleura and other diseases of the respiratory system) but no code for chronic respiratory disease.
      - Cough: An ICD 10 code of R05 but none of the above codes for respiratory disease.
      - Abnormal breathing: An ICD 10 code of R06 but none of the above codes for respiratory disease or cough.
    - Sports:
      - ICD 10 code of Z02.5 (examination for participation in sport)
      - ICD 10 code of Z10.3 (routine general health check-up of sports teams)
      - ICD 10 code of R69 (unknown and unspecified causes of morbidity) in combination with a medical event text that contains the search string 'sport', excluding 'transport' and 'dysport'.
      - ICD 10 code of Z71.8 (other specified counselling) in combination with a medical event text that contains the search string 'sport', excluding 'transport'.
      - ICD 10 code of Z71.8 (other specified counselling) in combination with a medical event text that contains the search string 'leistung', excluding 'reisemedizin', 'wunschleistung', 'sozialleistung', 'schulleistung', 'rehabilitationsleistung', 'sonderleistung', and 'gesundheitsleistung'.

- ICD 10 code Z02.7 (issue of medical certificate) in combination with a medical event text that contains the search string 'sport', excluding 'transport'.
  - ICD 10 code Z02.8 (other examinations for administrative purposes) in combination with a medical event text that contains the search string 'sport'.
- Anabolic steroids:
  - ICD 10 code of T38.7 (poisoning by androgens and anabolic congeners).
- Musculoskeletal:
  - ICD 10 code of M (diseases of the musculoskeletal system and connective tissue)
- Multiple unspecified injuries:
  - ICD 10 code T070
- Food or weight:
  - ICD 10 code of Z71.3 (dietary counselling and surveillance)
  - ICD 10 code of E66 (obesity)
  - ICD 10 code of E68.0 (sequelae of hyperalimentation)
  - ICD 10 code of R63 (symptoms and signs concerning food and fluid intake)
  - ICD 10 code or R64 (cachexia)
  - ICD 10 code of R62.8 (other lack of expected normal physiological development)
  - ICD 10 code R69 (unknown and unspecified causes of morbidity) in combination with a medical event text that contains the search string 'gewicht', excluding 'gleichgewicht' and 'urine spez'.
- Poisoning by certain substances:
  - ICD 10 code T39 (poisoning by nonopioid analgesics, antipyretics and antirheumatics)
  - ICD 10 code T40 (poisoning by narcotics and psychodysleptics)
  - ICD 10 code T42.4 (poisoning by benzodiazepines)
  - ICD 10 code T43 (poisoning by psychotropic drugs not elsewhere classified)
- Poisoning by beta-2-agonists:
  - ICD 10 code T44.5
- Drug-induced headache:
  - ICD 10 code G44.4
- Alcohol abuse:
  - ICD 10 code F10 (mental and behavioural disorders due to use of alcohol)
  - ICD 10 code Z50.2 (alcohol rehabilitation)
  - ICD 10 code Z71.4 (alcohol abuse counselling and surveillance)
- Abuse of other dependence producing substances:
  - ICD 10 code F11 (mental and behavioural disorders due to use of opioids)
  - ICD 10 code F12 (mental and behavioural disorders due to use of cannabinoids)
  - ICD 10 code F13 (mental and behavioural disorders due to use of sedatives or hypnotics)
  - ICD 10 code F14 (mental and behavioural disorders due to use of cocaine)
  - ICD 10 code F15 (mental and behavioural disorders due to use of other stimulants, including caffeine)

- ICD 10 code F16 (mental and behavioural disorders due to use of hallucinogens)
  - ICD 10 code F17 (mental and behavioural disorders due to use of tobacco)
  - ICD 10 code F18 (mental and behavioural disorders due to use of volatile solvents)
  - ICD 10 code F19 (mental and behavioural disorders due to use of multiple drug use and use of other psychoactive substances)
  - ICD 10 code Z71.5 (drug abuse counselling and surveillance)
  - ICD 10 code Z50.3 (drug rehabilitation)
  - ICD 10 code Z86.4 (personal history of psychoactive substance abuse)
  - ICD 10 code R69 (unknown and unspecified causes of morbidity) in combination with a medical event text that contains the search string 'abus'
- Abuse of non-dependence producing substances:
  - ICD 10 code F55
- Personal history of other specified risk factors:
  - ICD 10 code Z91.8
- Problems related to education or literacy:
  - ICD 10 code Z55
- Analysis (as applicable)
  - Type of analysis: Cohort study focusing on baseline factors. There will be no analysis of events that occur after start of treatment.
  - Measure of occurrence: Not applicable.
  - Measure of association:
    - The proportion of patients with each of the respiratory disorders on the date of the first prescription for a beta-2-agonist
    - The proportion of patients with an identified risk factor ever prior to and up to the date of the first prescription for a beta-2-agonist by type of risk factor:
      - Sports
      - Anabolic steroids
      - Musculoskeletal
      - Multiple unspecified injuries
      - Food or weight
      - Poisoning by certain substances
      - Poisoning by beta-2-agonists
      - Drug-induced headache
      - Alcohol abuse
      - Abuse of other dependence producing substances
      - Abuse of non-dependence producing substances
      - Personal history of other specified risk factors
      - Problems related to education or literacy
    - The proportion of patients with combinations of risk factors might also be considered
    - Mean age at start of treatment
    - Gender at start of treatment
  - Stratified analyses: Results will be stratified by speciality.
  - Confounders (with codes): Not applicable.
  - Statistical model: The analysis will be descriptive.
  - Handling of missing data: Not applicable.
  - Sensitivity analyses: No sensitivity analyses are planned.