Guidelines for applications under the well established medicinal use (bibliographical) simplified procedure

1. Introduction

These guidelines are derived from the relevant sections of Annex 1 analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (as amended) to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

2. Definition of well established medicinal use

‘Well established medicinal use’ is the reference to the constituent(s) of a medicinal product that has/have a historically proven acceptable level of safety and with recognised efficacy based on the following criteria:

2.1 the time over which a substance has been used with regular application in patients;
2.2 quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other valid methods;
2.3 the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments;
2.4 the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than ten years from the first systematic and documented use of that substance as a medicinal product or thirty years in the case of herbal medicinal products.

3. Well Established Medicinal Use documentation requirements

For medicinal products that meet the definition of well established medicinal use, the applicant shall submit the following data:

3.1 CTD Module 1 – Administrative information, with particular reference to Module 1 Section 1.5 – specific requirements for different types of applications, 1.5.1 – information for bibliographical applications. In this section a concise document (up to 5 pages) should be provided that summarises the grounds and evidence used for demonstrating that the constituent(s) of the medicinal product have a well established use with an acceptable level of safety and efficacy;

3.2 CTD Module 2 – CTD summaries;

3.3 CTD Module 3 – chemical, pharmaceutical and biological information;

3.4 For Module 4–non clinical reports and Module 5 - clinical reports, a detailed scientific bibliography shall be presented that addresses the following aspects:
(i) factors described in 2.1, 2.2, 2.3 and 2.4 above;

(ii) documentation submitted by the applicant should cover all aspects of the safety assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, should be communicated;

(iii) particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking;

(iv) the non-clinical overview must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product which will be granted a marketing authorisation in spite of the existing differences;

(v) post-marketing experience with other products containing the same components is of particular importance and applicants should put a special emphasis on this issue.

Kosovo Medicines Agency