European Medicines Agency
Evaluation of Medicines for Human Use

London, 24 May 2006
EMEA/CHMP/BWP/124446/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON POTENCY LABELLING FOR INSULIN ANALOGUE CONTAINING PRODUCTS *WITH PARTICULAR REFERENCE TO THE USE OF "INTERNATIONAL UNITS" OR "UNITS"*

DRAFT AGREED BY BWP	March 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	21 April 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2005
AGREED BY EWP	April 2006
AGREED BY BWP	May 2006
ADOPTION BY CHMP	1 June 2006
DATE FOR COMING INTO EFFECT	1 December 2006

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INTRODUCTION

Insulin analogues are a group of insulin molecules where the molecular structure of human insulin has been modified. These modifications could be a removal, an addition or replacement of one, or a few, amino acids in the molecule, which are achieved by changes in the gene, or other chemical modifications. The purpose of the molecular modifications is to alter the *in vivo* properties e.g. the absorption rate of human insulin to obtain for instance a faster or slower action of the insulin.

Recent Marketing Authorisation applications have featured differences between the units employed by manufacturers for expressing the potencies of medicinal products containing insulin analogues, including the manner in which the potency units are expressed in the information provided for these products. These observations raise the following questions:

- What are the correct units for expressing the potencies of these preparations? Or
- Is IU an appropriate unitage for expressing insulin analogues potency?

1. RECOMMENDATION

There are two salient issues:

- The International Standard for human insulin has been developed solely for use in the determination of the potency of human insulin products and its development did not encompass its use for the purpose of determining the potencies of insulin analogues.
- Insulin analogues may differ significantly from non-derivatised human insulin with respect to their pharmacokinetic and pharmacodynamic properties.

Quality aspects

Labelling with International Units (IU) should exclusively be used for those insulins for which an International Standard has been established, e.g. human insulin. As a consequence, unless an International Standard is established for an insulin analogue, potency should be labelled and reported as in-house units.

This recommendation is in line with ICH guideline Q6B:
"The results of biological assay should be expressed in units of activity calibrated against an international or national reference standard. Where no such reference standard exists, a characterised in-house reference material should be established and assay results reported as in-house units."

Labelling / SPC aspects

As the in-house units established for insulin analogues are active substance specific units, one analogue unit may not be equivalent to one IU of human insulin or one unit of a different insulin analogue. It is therefore recommended that the SPC and package leaflet for insulin analogues should include an appropriate explanation of this issue as it applies to the particular product concerned, for example:

- "The potency of this preparation is stated in units. These units are exclusive to <product name> and are not the same as IU or the units used to express the potency of other insulin analogues. See section 5.1 (Pharmacodynamics)"

The statement above should be included at the beginning of SmPC section 4.2 "Posology and Methods of Administration".

It is further recommended that the SPC and package leaflet for insulin analogues include special warnings for changing from one preparation to another, for example:

"Switching a patient to another type or brand of insulin should be done under strict medical supervision and may require a change in dose."

This statement should be included in SmPC section 4.4 "Special warnings and special precautions for use".