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3 Pharmacovigilance Risk Assessment Committee (PRAC)

4 Risk minimisation strategy for high strength and fixed 5 combination insulin products

6 Draft addendum to the good practice guide on risk minimisation and
7 prevention of medication errors¹

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8 Comments should be provided using this [template](#). The completed comments form should be sent to medicationerrors2013@ema.europa.eu by 14 June 2015.

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27 **Introduction (background)**

28 Following the recent approval of a number of high strength insulins (i.e. higher than EU-wide standard
29 100 units/ml concentration) in the EU either as new medicinal products or as line extensions of existing
30 medicines, and the approval of a fixed combination of insulin with another non-insulin injectable blood
31 glucose lowering agent, concerns about potential medication errors were raised by the European
32 Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC). To pro-actively address
33 the risk of errors with this type of insulin products in a harmonised way and to avoid significant over-
34 or under-dosing as clinical consequence of errors, a single strategy to minimise the potential risk of
35 medication errors was developed by a dedicated PRAC drafting group and is documented here. This
36 strategy may be further revised as experience with high strength and novel insulin-containing products
37 accumulates.

38 **1. Scope**

39 In the context of the evaluation procedures of novel higher than standard (100 units/ml) strength
40 insulin products and fixed combinations of insulin with another non-insulin injectable blood glucose
41 lowering agent, input from patients and healthcare professionals as well as experts on medication
42 errors was collected regarding the design and use of pre-filled insulin pens, the packaging design, the
43 product information and the educational material for patients and healthcare providers. This has led to
44 the identification of a set of risk minimisation measures that may be applicable to any high strength
45 insulin/fixed combination insulin product. Applicants should consider these measures at the earliest
46 stage during development and design to minimise the risk of medication errors. This guidance should
47 also support national competent authorities and the PRAC in the benefit-risk evaluation of new high
48 strength insulin/fixed combination insulin products, taking into account their place in diabetes therapy
49 and existing treatment options.

50 Given the different healthcare settings in Europe, the organisation and management of diabetes
51 treatment may vary across Member States and consequently the need for additional risk minimisation
52 measures in respective healthcare settings may also vary. This guidance provides a common set of risk
53 minimisation measures implementable in all EU Member States to reduce the risk of medication errors
54 with new high strength insulins/fixed combination insulins.

55 Marketing authorisation holders and applicants are encouraged to use this guidance as a checklist to
56 ensure that the risk of medication errors is addressed consistently for all high strength insulins/fixed
57 combination insulins and in line with the regulatory requirements specified in GVP Module V on risk
58 management planning and GVP Module XVI on risk minimisation measures: selection of tools and
59 effectiveness indicators.

60 The common elements for risk minimisation and the key safety messages provided in tables 3 and 4
61 (see chapter 4) for both healthcare professionals and patients are based on the following assumptions:

- 62 a) The high strength insulin or the fixed combination insulin product is manufactured in pre-filled pens
63 only. No other pharmaceutical presentations such as vials or cartridges are made available under
64 the same marketing authorisation.
- 65 b) The pre-filled pen referred to under a) automatically adjusts for strength and no dose conversion
66 or re-calculation is required when switching between standard strength (100 units/ml) and higher
67 strength or fixed combination insulin products within the same product range.
- 68 c) Bioequivalence between different strengths has been demonstrated and a dose of 100 units has
69 the same therapeutic effect when taken from standard (100 units/ml) or higher strength injectable

70 insulin solutions. If bioequivalence cannot be achieved the applicant should consider additional risk
71 minimisation measures in line with the provisions in chapter 5.

72 d) For products where insulin is combined with another injectable blood glucose-lowering agent in a
73 prefilled pen, the number of 'dose steps' is always equivalent to the number of units of insulin to
74 be administered, i.e. the dose counter window on the pen will display the number of dose steps
75 and this will be the same as the number of units of insulin.

76 For the purpose of planning and implementation of risk minimisation measures in line with GVP module
77 V the list of potential medication errors in table 1 and the proposed routine risk minimisation measures
78 included in chapter 3 are considered specific to medicinal products with an insulin strength higher than
79 standard 100 units/ml or for medicinal products with a fixed combination of an insulin with another
80 non-insulin injectable blood glucose lowering agent respectively. In this context a new product is
81 defined as a new insulin (new INN) or a new pharmaceutical presentation of an authorised insulin
82 product in a higher than standard (100 units/ml) strength, or a new fixed combination of an insulin
83 with another non-insulin injectable blood glucose lowering agent.

84 However, this list of potential medication errors in table 1 is not exhaustive and careful case-by-case
85 evaluation of the need for further additional measures in line with the provisions of GVP module XVI to
86 address other risks of medication errors is warranted, particularly if any of the assumptions a) or b)
87 above with regard to the development and design of the pen device cannot be met. Marketing
88 authorisation holders and applicants are strongly recommended to liaise with the competent authorities
89 in Member States and the Agency for pre-submission guidance on these aspects.

90 2. Potential for medication errors

91 Based on the list of potential medication errors that may occur with new high strength insulin/fixed
92 combination insulin products presented in table 1, this guidance aims to address the key elements for
93 risk mitigation including recommendations for the design of the product, the naming and packaging
94 and the routine and additional risk minimisation measures. Marketing authorisation holders or
95 applicants should provide a justification for any of the potential medication errors listed in table 1 not
96 being addressed as a safety concern in the EU Risk Management Plan.

97 **Table 1:** Potential medication errors to be considered for **high strength/ fixed combination insulin products**

<input checked="" type="checkbox"/> Medication error	
<input type="checkbox"/>	Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins, including by visually impaired or colour blind patients with diabetes mellitus;
<input type="checkbox"/>	Medication error due to mix-up between different product strengths, including by visually impaired or colour blind patients with diabetes mellitus;
<input type="checkbox"/>	Medication error due to non-compliance with instructions for use: unnecessary dose re-calculation;
<input type="checkbox"/>	Medication error associated with switching patients between standard 100 units/ml and higher units/ml strength insulin products;
<input type="checkbox"/>	Misuse related to extraction of insulin from the pre-filled pen using a syringe;
<input type="checkbox"/>	Medication error due to non-compliance with instructions to use a new needle for each injection: this can lead to blockage of needle and subsequent injection of wrong dose;
<input type="checkbox"/>	Medication error associated with switching from conventional insulin to fixed combination of insulin with another injectable blood glucose lowering agent and vice versa;

98 **3. Routine risk minimisation**

99 **3.1. Drug product design characteristics**

100 The high strength/fixed combination insulin product should be manufactured in a pre-filled insulin
101 injector device only. The insulin injector device should be a multiple-dose, disposable insulin pen
102 injection system for single patient use for either self-injection or to be operated by a healthcare
103 professional, patient relative or carer. The insulin injector device should be discarded when the insulin
104 container is empty.

105 The injector design should provide a dosing mechanism for accurately injecting a selected dose of
106 insulin through a single hypodermic needle and enable repeated dispensing of fixed doses according to
107 the therapeutic requirements by means of an integrated dosage selector and injection button. An
108 integrated dose counter window should display the dose in units irrespective of strength or
109 concentration of the insulin solution for injection to avoid medication errors due to unnecessary dose
110 recalculation. The maximum insulin dose per injection should be limited to avoid serious overdose.

111 For pre-filled pens where the same active substance is available in different strengths, the dose steps
112 should be the same for all strengths, i.e. one dose step corresponds to one unit of insulin at 100
113 units/ml, 200 units/ml, 300 units/ml etc.

114 For fixed combination insulin products the dose counter window should display the number of dose
115 steps. The number of dose steps should be equivalent to the number of units of insulin to be injected.
116 To ensure consistency with existing insulin products, one dose step of a fixed combination insulin pre-
117 filled pen should contain one unit of insulin.

118 The injector device should consist of an irreversibly integrated insulin cartridge as primary packaging
119 for the insulin solution for injection which cannot be replaced, a cap for the safety of the patient and to
120 protect the cartridge, the cartridge holder and the dosing mechanism. The device may be operated
121 fully mechanically or may include electronic components.

122 **3.2. Naming and pack design**

123 Pack design and labelling ensure that the critical information necessary for the safe use of a medicine
124 is legible, easily accessible and that users of medicines can easily assimilate this information so that
125 any risk of confusion and error is minimised².

126 The information which should be included on the labelling and package leaflet is provided in Title V of
127 Directive 2001/83/EC. In addition, the details on the display and readability of such information on the
128 printed materials are included in the guideline on the readability of the labelling and package leaflet of
129 medicinal products for human use² (hereinafter 'readability guideline').

130 Also, the guidance on the criteria applied by the Name Review Group (NRG) when reviewing the
131 acceptability of proposed (invented) names for medicines (for the centralised procedure) and the
132 details on the overall procedure for submitting and checking the acceptability of proposed (invented)
133 names are included in the guideline on the acceptability of names for human medicinal products
134 processed through the centralised procedure (Revision 6, 22 May 2014).

² Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, 12 January 2009)

135 In addition to the guidelines above-mentioned, applicants and marketing authorisation holders are
 136 encouraged to consider new invented names for new high strength/fixed combination insulins to
 137 minimise the risk of medication errors when selecting the invented name and when preparing the
 138 mock-ups and specimens of the sales presentations³.

139 Further to the review of the invented names and mock-ups of the most recently evaluated/approved
 140 high strength/fixed combination insulins, specific recommendations issued for this type of insulin
 141 products are summarised in table 2.

142 **Table 2:** Recommendations on naming and pack design for **high strength insulin/fixed combination insulin**
 143 **products** addressing the risk of potential medication errors.

Medication error	Recommendation on naming and pack design
Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins, including by visually impaired or colour blind patients with diabetes mellitus;	<ul style="list-style-type: none"> • Invented name selection <ul style="list-style-type: none"> – Careful consideration should be given to the selection of the invented name as part of applicant’s strategy to avoid mix-ups. • Name of the medicine (invented name, strength and pharmaceutical form): <ul style="list-style-type: none"> – To appear prominently displayed across the labelling and using a sufficiently large font type on prime spaces, particularly on the front panel. – The invented name should appear more prominently displayed than the device name to avoid confusion.
Medication error due to mix-up between different product strengths, including by visually impaired or colour blind patients with diabetes mellitus;	<ul style="list-style-type: none"> • Strength: <ul style="list-style-type: none"> – The concentration must appear prominently displayed using a large font and allowing enough contrast between the font and the background colour. Colours should be chosen to enhance recognition and ensure a good contrast between the text and the background to assure maximum legibility and accessibility of the information⁴. – The location of the product strength should preferably be next to the invented name to encourage the inclusion of it as part of the prescription. – Units to be spelled in full and using lower case so it is not mistaken as the number 0 or 4, causing a 10-fold overdose or greater (e.g., 4U seen as “40” or 4u seen as “44”)⁵. • Active substance <ul style="list-style-type: none"> – To appear prominently displayed across the labelling. – Use of formatting should be considered to distinguish products with a similar-sounding active substance. • Design features and use of colour <ul style="list-style-type: none"> – Careful consideration should be given to the pack design as part of applicant’s strategy to avoid mix-ups, especially when a common pack design is being used by the same MAH. It is recommended to add and enhance design features to optimally distinguish the new

³ A ‘mock-up’ is a copy of the flat artwork design in full colour, presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging so that the three dimensional presentation of the label text is clear. A ‘specimen’ is a sample of the actual printed outer and immediate packaging materials and package leaflet (i.e. the sales presentation)

⁴ Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, 12 January 2009)

⁵ ISMP’s List of Error-Prone Abbreviations, Symbols and Dose Designations (<http://www.ismp.org/tools/errorproneabbreviations.pdf>)

Medication error	Recommendation on naming and pack design
	<p>product from others with the same/different MAH taking into account possible errors from look-alike product livery.</p> <ul style="list-style-type: none"> – Colour is recommended to clearly distinguish between insulins/strengths and to draw attention to specific information on the label, particularly to enhance recognition of the high strength. <ul style="list-style-type: none"> • Device <ul style="list-style-type: none"> – Any colour differentiation used on the labelling should be also carried onto the device e.g. whole colour used for the pre-filled pen or push button or glass barrel etc. – Careful consideration should be given to the colour chosen for the device as part of applicant's strategy to avoid mix-ups. For example, avoiding the use of the same colour in light or dark shades. – The colour of the device should be very different, especially for visually impaired or colour blind patients with diabetes mellitus.
Medication error due to non-compliance with instructions for use: unnecessary dose recalculation	<p>Warnings</p> <p>It is recommended to highlight the warnings in a prominent way and on the main panels.</p>
Medication error associated with switching patients between standard 100 units/ml and higher units/ml strength insulin products	Not applicable.
Misuse related to extraction of insulin from pen using a syringe	<p>Warnings</p> <p>It is recommended to highlight the warnings in a prominent way and on the main panels, if feasible.</p>
Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle	<p>Warnings</p> <p>It is recommended to highlight the warnings in a prominent way and on the main panels, if feasible.</p>

144 **3.3. Summary of product characteristics (SmPC), package leaflet (PL) and**
145 **labelling**

146 To minimise the risk of medication errors all new marketing authorisation applications for insulin
147 products described in chapter 1 should include as a minimum the safety messages outlined in table 3
148 in the SmPC and PIL respectively. References to relevant SmPC sections should be included in the EU
149 Risk Management Plan, Part V Risk Minimisation Measures for each medication error.

150

151 **Table 3:** Medication error related safety messages in the product information of **high strength/fixed**
 152 **combination insulin products**

Medication error	Routine risk minimisation in SmPC and PIL
Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins, including by visually impaired or colour blind patients with diabetes mellitus	<p>SmPC section 4.4 and PIL section 2 under 'Warnings and precautions' and section 3</p> <ul style="list-style-type: none"> Warning of medication errors where short-acting insulins have been accidentally mixed-up with long-acting insulins. Need to always check the label of the insulin pen before each injection to avoid accidental mix-ups between long-acting and short-acting insulins.
Medication error due to mix-up between different product strengths, including by visually impaired or colour blind patients with diabetes mellitus	<p>SmPC section 4.2 and PIL section 3</p> <ul style="list-style-type: none"> Explain that the product is available in two strengths and no dose re-calculation is required. <p>SmPC section 4.4 and PIL section 2 under 'Warnings and precautions' and section 3</p> <ul style="list-style-type: none"> Need to always check the label of the insulin pen before each injection to avoid accidental mix-ups between 2 [or more] different strengths of insulins. <p>SmPC section 6.6 and PIL section 3</p> <ul style="list-style-type: none"> Explain how the strength is highlighted on the product packaging.
Medication error due to non-compliance with instructions for use: unnecessary dose recalculation	<p>SmPC section 4.2 and PIL section 3</p> <ul style="list-style-type: none"> Explain that the pre-filled pen has been specifically designed for the concerned insulin product, therefore no dose re-calculation is required. The SmPC wording should be carefully chosen to avoid misinterpretation.
Medication error associated with switching patients between standard 100 units/ml and higher units/ml strength insulin products	<p>SmPC section 4.2 and PIL section 2 under 'Warnings and precautions' and section 3</p> <ul style="list-style-type: none"> The user should carefully follow the instructions for starting different strength insulins or switching from standard to different strength insulins. The dose counter shows the number of units to be injected and no dose conversion is required when transferring a patient to a new strength. Close blood glucose monitoring is recommended during the transition and in the initial weeks thereafter.
Misuse related to extraction of insulin from pen using a syringe	<p>SmPC section 4.2 and PIL section 3</p> <ul style="list-style-type: none"> Explain that the product must not be drawn from the glass barrel of the pre-filled pen into a syringe (see section 4.4). <p>SmPC section 4.4 and PIL section 3</p> <ul style="list-style-type: none"> To avoid dosing errors and potential overdose, the patients must also be instructed to never use a syringe to draw the product from the glass barrel of the pre-filled pen into a syringe. <p>Labelling outer carton section 7 and label section 6</p> <ul style="list-style-type: none"> To state that the insulin should only be used in the pre-filled pen.

Medication error	Routine risk minimisation in SmPC and PIL
Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle	<p>SmPC section 4.2, PIL section 3 and labelling outer carton section 7 and label section 6</p> <ul style="list-style-type: none"> Instruct patients to always use a new needle. The re-use of insulin pen needles increases the risk of blocked needles which may cause under- or overdosing. <p>SmPC section 6.6 and PIL section 3</p> <ul style="list-style-type: none"> A new needle must always be attached before each use. Needles must not be re-used. <p>SmPC sections 4.4 and 6.6 and Instructions For Use (IFU)</p> <ul style="list-style-type: none"> In the event of blocked needles patients must follow the instructions described in the Instructions for Use accompanying the package leaflet.
Medication error associated with switching from conventional insulin to fixed combination of insulin with another injectable blood glucose lowering agent	<p>SmPC section 2 and PIL section 6</p> <ul style="list-style-type: none"> Qualitative and quantitative composition per ml solution of product. <p>SmPC section 4.2 and PIL section 3</p> <ul style="list-style-type: none"> Explain how the dose is calculated when using a fixed combination product compared to standard units for mono insulin products. Explain how the dose counter on the pre-filled pen shows the number of units of insulin.

153 **3.4. Regulatory requirements for user testing**

154 High strength insulin medicinal products or new fixed combinations of insulin analogue and other blood
155 glucose lowering agents submitted as a new marketing authorisation application should comply with
156 Articles 59(3), 61(1) and 63(2) of Directive 2001/83/EC. User consultation should be carried out to
157 demonstrate the readability and usefulness of the package leaflet to patients according to the current
158 requirements. When such consultation is conducted, critical sections of the leaflet as well as the key
159 safety messages identified in this document should specifically be tested.

160 This is also applicable to high strength insulin formulations submitted as line extension of existing
161 insulin products. This case would be considered to be a significant change of the package leaflet of an
162 existing marketing authorisation, as per the readability guideline.

163 **4. Key safety messages for healthcare professionals and**
164 **patients**

165 For each potential medication error listed in table 1, the key safety messages for healthcare
166 professionals and patients are provided in table 4 (high strength insulin products) and table 5 (fixed
167 combination insulin products) below. Marketing authorisation holders should address these key safety
168 messages with the routine risk minimisation measures referred to in chapter 3.

169

Medication error	Healthcare professionals key safety messages	Patients key safety messages
<p>Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins, including by visually impaired or colour blind patients with diabetes mellitus;</p>	<ul style="list-style-type: none"> • There is a risk of medication errors due to mix-up between long-acting (basal) and short-acting (bolus) insulin products. • Always check the insulin label before each injection to avoid accidental mix-ups between long-acting (basal) and short-acting (bolus) insulin products. • Need for prescriber, nurse or pharmacist to explain to the patient the key differences in appearance of the different short- and long acting insulin products that are being prescribed. 	<ul style="list-style-type: none"> • Always check the insulin label before each injection to avoid accidental mix-ups between long-acting (basal) and short-acting (bolus) insulin products
<p>Medication error due to mix-up between different product strengths, including by visually impaired or colour blind patients with diabetes mellitus;</p>	<ul style="list-style-type: none"> • Inform about launch of higher strength insulin <PRODUCT NAME> and availability of two [or more] strengths. • Key features and differences of the design of the packages and the prefilled pen devices between the two strengths with focus on colour coding, warning statements on carton and other safety design features⁶ [as applicable]. • There is a risk of medication errors due to mix-up of different strengths available for <PRODUCT NAME>. • To encourage prescribers to always include the correct strength on the prescription. • Healthcare professional awareness of the need to prescribe the insulin dose in units and the dose frequency for <PRODUCT NAME>. Encourage 	<ul style="list-style-type: none"> • <PRODUCT NAME> is now available in two [or more] strengths; • Key features and differences of the design of the packages and pre-filled pen devices; • Always check the insulin label before each injection to avoid accidental mix-ups between the [2] different strengths of <PRODUCT NAME>;

⁶ E.g. colour graphics which should be included in the educational materials.

	<p>healthcare professionals to always spell out 'units' in full and using lower case so it is not mistaken as the number 0 or 4, causing a 10-fold overdose or greater.</p> <ul style="list-style-type: none"> • Always check the insulin label before each injection to avoid accidental mix-ups between the [2] different strengths of <PRODUCT NAME>. • Pharmacists should be aware that insulins are now available in different strengths. • Pharmacists are recommended to ask patients/carers to visually identify the strength of insulin dispensed in order to ensure patients/carers are able to read the dose counter of the pen device. 	
<p>Medication error due to non-compliance with instructions for use: unnecessary dose recalculation</p>	<ul style="list-style-type: none"> • The dose counter of the <PRODUCT NAME> pen device shows the number of units of insulin irrespective of strength and no dose conversion is necessary. 	<ul style="list-style-type: none"> • The dose counter of the <PRODUCT NAME> pen device shows the number of units of insulin irrespective of strength and no dose conversion is necessary. • Always use the dose counter and the dose pointer to select the dose.
<p>Medication error associated with switching patients between standard 100 units/ml and higher units/ml strength insulin products</p>	<ul style="list-style-type: none"> • No dose re-calculation (i.e. dose conversion) when transferring patients from standard strength 100 units/ml insulin <PRODUCT NAME> to higher strength [X] units/ml <PRODUCT NAME> should be performed. • Need for close glucose monitoring during the transfer to high-strength insulin and in the following weeks; • Consider adjustment of doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant 	<ul style="list-style-type: none"> • Dose conversion on switching patients from standard strength 100 units/ml insulin <PRODUCT NAME> to higher strength [X] units/ml <PRODUCT NAME> should generally not be performed unless otherwise instructed by the prescriber for an individual insulin product; • Need for close glucose monitoring during the transfer to high-strength insulin and in the following weeks as instructed by the prescriber;

	antidiabetic treatment.	
Misuse related to extraction of insulin from pen using a syringe	<ul style="list-style-type: none"> • <PRODUCT NAME> should only be used with the pre-filled pen device in which it is supplied; • Healthcare staff must never use a syringe to withdraw insulin from a pre-filled pen; 	<ul style="list-style-type: none"> • <PRODUCT NAME> should only be used with the pre-filled pen device in which it is supplied; • Patients must never use a syringe to withdraw insulin from a pre-filled pen;
Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle	Routine risk minimisation, see table 3.	Routine risk minimisation, see table 3.

171 **Table 5:** Key safety messages for **fixed combination insulin products** addressing the risk of medication errors.

Medication error	Healthcare professional key safety messages	Patients key safety messages
Medication error associated with switching from conventional insulin to fixed combination of insulin with another injectable blood glucose lowering agent	<ul style="list-style-type: none"> • <PRODUCT NAME> contains a fixed combination of insulin and [injectable blood glucose lowering agent]; • Explanation of the posology of <PRODUCT NAME>; • Definition of one dose step of <PRODUCT NAME>; • Prescribers should state the number of dose steps to be injected, and the dose frequency, on the prescription; • The dose counter window of the prefilled pen displays the number of dose steps to be injected; • Close monitoring of blood glucose is recommended on initiation of the product and in the following weeks; 	<ul style="list-style-type: none"> • Explanation of one dose step of <PRODUCT NAME>. • Your doctor will prescribe the number of dose steps to be injected; • The dose counter window on the prefilled pen displays the number of dose steps to be injected; • Close monitoring of blood glucose is recommended on initiation of the product and in the following weeks;

172 **5. Additional risk minimisation measures**

173 To minimise the risk of medication errors associated with high strength and fixed combination insulin
174 products, applicants and marketing authorisation holders should adequately address the potential
175 medication errors described in chapter 2 with routine risk minimisation measures taking into account
176 the key safety messages in chapters 3 and 4. Marketing authorisation holders and applicants should
177 ensure that all options towards optimising the product design, naming, packaging and labelling to
178 prevent medication errors have been sufficiently explored.

179 There may be **exceptional circumstances** where the assumptions a) to d) referred to in chapter 1
180 cannot be met and where additional key safety messages not included in tables 4 and 5 are considered
181 necessary to mitigate the risk of medication errors with high strength insulin/fixed combination insulin
182 products (e.g. if bioequivalence between a standard 100 units/ml strength insulin product and its
183 higher strength extension cannot be demonstrated). In these circumstances, the following additional
184 risk minimisation measures should be considered in the EU Risk Management Plan (Part V Risk
185 Minimisation Measures) in combination with relevant additional key safety messages for healthcare
186 professionals and patients:

- 187 • A **healthcare professional guide** targeted to all healthcare professionals who are expected to
188 prescribe, dispense or administer the product;
- 189 • A **patient guide** targeted to all patients who use the product.

190 ***5.1. Conditions or restrictions with regard to the safe and effective use***

191 Where additional risk minimisation measures are deemed necessary these should be reflected in the
192 conditions or restrictions with regard to the safe and effective use for new or existing insulin products
193 described in chapter 2 (Annex II.D of the marketing authorisation):

194 Prior to the use of <PRODUCT NAME> in each Member State the Marketing Authorisation
195 Holder (MAH) must agree the content and format of the educational programme, including
196 communication media, distribution modalities, and any other aspects of the programme, with
197 the National Competent Authority.

198 The educational programme is aimed at increasing awareness about the risk of medication
199 errors during treatment with <PRODUCT NAME> and providing guidance on the correct use.

200 The MAH shall ensure that in each Member State where <PRODUCT NAME> is marketed, all
201 healthcare professionals who are expected to prescribe, dispense or administer <PRODUCT
202 NAME> are provided with the following educational package:

- 203 • Healthcare professional educational material

204 The healthcare professional educational material should contain the following elements:

- 205 • The Summary of Product Characteristics (SmPC)
- 206 • The Healthcare Professional guide
- 207 • The Patient guide

208 The Healthcare Professional guide shall contain the following key messages:

- 209 • The need to provide patients with the patient guide prior to prescribing or dispensing
210 <PRODUCT NAME>.

211 • <[List key messages for healthcare professionals of chapter 4 and 5 for safety concerns as
212 applicable]>

213 • <>

214 The Patient guide shall contain the following key messages:

215 • <[List key messages for patients of chapter 4 and 5 for safety concerns as applicable]>

216 • <>

217 **5.2. Effectiveness measures**

218 Marketing authorisation holders should follow the guidance provided in GVP Module XVI on risk
219 minimisation measures: selection of tools and effectiveness indicators (Rev 1) for effectiveness
220 measures to be included in the EU Risk Management Plan.

221 **6. Recommendations for clinical management and storage**

222 Healthcare professionals are encouraged to

- 223 • risk assess electronic and paper systems used to prescribe, dispense and administer high-
224 strength/fixed combination insulin products,
- 225 • carefully check the product strength selected in electronic systems and
- 226 • risk assess storage arrangements for high-strength/fixed combination insulin products to help
227 ensure selection of the correct strength and to avoid confusion with other products.