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Pharmacovigilance Risk Assessment Committee (PRAC)

Risk minimisation strategy for high-strength and fixed-combination insulin products

Addendum to the good practice guide on risk minimisation and prevention of medication errors¹

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Introduction (background)

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

1. Scope

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

Given the different healthcare settings in Europe, the organisation and management of diabetes treatment may vary across Member States and as a consequence risk minimisation measures in respective healthcare settings may also vary. This guidance provides a common set of risk minimisation measures implementable in all EU Member States to harmonise the management of the risk of medication errors associated with new high-strength insulins/fixed-combination insulins.

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

The common elements for risk minimisation provided in chapter 3 and the safety communication for healthcare professionals, patients and carers in chapter 5 are based on the following assumptions:

- a) The high-strength insulin or the fixed-combination insulin product is manufactured in pre-filled pens only unless duly justified in exceptional circumstances. No other pharmaceutical presentations such as vials or cartridges should be made available under the same marketing authorisation the use of which may be associated with a higher risk of medication errors.
- b) The pre-filled pen referred to under a) automatically adjusts for strength and no dose conversion or re-calculation is required when switching between standard strength (100 units/ml) and higher strength or fixed-combination insulin products within the same product range.
- c) Bioequivalence between different strengths has been demonstrated and a dose of 100 units has the same therapeutic effect when taken from standard (100 units/ml) or higher strength injectable

insulin solutions. If bioequivalence cannot be achieved the applicant should consider additional risk minimisation measures in line with the provisions in chapter 4.

- d) For products where insulin is combined with another injectable blood glucose-lowering agent in a prefilled pen, the number of 'dose steps' is always equivalent to the number of units of insulin to be administered, i.e. the dose counter window on the pen will display the number of dose steps and this will be the same as the number of units of insulin. If this cannot be achieved the applicant should consider additional risk minimisation measures in line with the provisions in chapter 4.

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

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

2. Potential for medication errors

The potential medication errors listed in table 1 have been associated with the use of novel high-strength insulin/fixed-combination insulin products but may also occur with other insulin containing products.

This guidance aims to address the key elements for risk mitigation including recommendations for drug product design, naming and packaging and routine and additional risk minimisation measures for high-strength insulins/fixed-combination insulins in line with its scope. Marketing authorisation holders and applicants should therefore address the potential medication errors listed in table 1 as safety concerns in the EU Risk Management Plan for the development of appropriate risk minimisation measures. Other potential medication errors may be added as applicable.

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 standard 100 units/ml and higher units/ml strength insulin products, 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 checked="" type="checkbox"/> Medication error	
<input type="checkbox"/>	Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle;
<input type="checkbox"/>	Medication error associated with switching between conventional insulin and fixed-combination of insulin with another injectable blood glucose lowering agent;
<input type="checkbox"/>	Other safety concerns related to medication errors as applicable;

3. Routine risk minimisation

3.1. Drug product design characteristics

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

The pre-filled pen design should provide a dosing mechanism for accurately injecting a selected dose of insulin through a single hypodermic needle and may enable repeated dispensing of fixed or flexible doses according to the therapeutic requirements by means of an integrated dosage selector and injection button. An integrated dose counter window should display the dose in units irrespective of strength or concentration of the insulin solution for injection to avoid medication errors due to unnecessary dose recalculation. The maximum insulin dose per injection should be limited to avoid accidental overdose taking into account the therapeutic needs of different patient populations who may use the pre-filled pen device.

For pre-filled pens where the same active substance is available in standard 100 units/ml and higher units/ml strength, the dose steps should be the same for all strengths, i.e. one dose step corresponds to one unit of insulin. For fixed-combination insulin products the dose counter window should display the number of dose steps. The number of dose steps should be equivalent to the number of units of insulin to be injected.

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

Ideally, pre-filled pen devices should provide an empty surface space for attaching patient name tags or dosing instructions without hiding the label or colour features.

3.2. Naming and pack design

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

The information which should be included on the labelling and package leaflet is provided in Title V of Directive 2001/83/EC. In addition, the details on the display and readability of such information on the

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

printed materials are included in the guideline on the readability of the labelling and package leaflet of medicinal products for human use² (hereinafter 'readability guideline').

Also, the guidance on the criteria applied by the Name Review Group (NRG) when reviewing the acceptability of proposed (invented) names for medicines (for the centralised procedure) and the details on the overall procedure for submitting and checking the acceptability of proposed (invented) names are included in the guideline on the acceptability of names for human medicinal products processed through the centralised procedure³.

In addition to the above-mentioned guidelines, marketing authorisation holders and applicants are encouraged to consider new invented names for new high-strength/ fixed-combination insulins to minimise the risk of medication errors when selecting the invented name and when preparing the mock-ups and specimens of the sales presentations⁴.

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

Table 2: Recommendations on naming and pack design for **high-strength insulin/ fixed-combination insulin 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. – To display the invented name also in Braille format. – The invented name should appear more prominently displayed than the device name to avoid confusion. • 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 information⁵. – The location of the product strength should preferably be next to the invented name to encourage the inclusion of it as part of the
Medication error due to mix-up between standard 100 units/ml and higher units/ml strength insulin products, including by visually impaired or colour blind patients with diabetes mellitus	

³ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500167844.pdf

⁴ 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)

⁵ Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, 12 January 2009)

Medication error	Recommendation on naming and pack design
	<p>prescription.</p> <ul style="list-style-type: none"> – 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 dosing error (e.g. if 4U is seen as "40")⁶. <ul style="list-style-type: none"> • 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 product from others with the same/different MAH taking into account possible errors from look-alike product livery. – Colour is recommended to clearly distinguish between insulins and to draw attention to specific information on the label, particularly to enhance recognition of the high-strength. • Device <ul style="list-style-type: none"> – Any colour differentiation used on the labelling should be carried onto the device or parts of it, e.g. on push button or glass barrel applying appropriate standards for user testing (see section 3.4.) to achieve differentiating designs. – Careful consideration should be given to the colour chosen for the device as part of applicant's strategy to avoid mix-ups. – The colour of the device should be very different, especially for visually impaired or colour blind patients with diabetes mellitus. – A palpable structure (e.g. ridge or thickening) on the pen device is recommended. – The provision of an empty surface for adhesive labels (e.g. for patient details) should not affect readability of the label or recognition of colour features.
<p>Medication error due to non-compliance with instructions for use: unnecessary dose recalculation</p>	<p>Warnings</p> <p>It is recommended to highlight the warnings in a prominent way and on the main panels of the outer carton.</p>
<p>Medication error associated with switching patients between standard 100 units/ml and higher units/ml strength insulin products</p>	<p>Warnings</p> <p>If under the same marketing authorisation bioequivalence between standard 100 units/ml and higher units/ml strength insulin products cannot be demonstrated, it is recommended to highlight relevant warnings in a prominent way on the main panels of the outer carton.</p>

⁶ 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
Misuse related to extraction of insulin from pen using a syringe	Warnings It is recommended to highlight the warnings in a prominent way and on the main panels of the outer carton, if feasible.
Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle	Warnings It is recommended to highlight the warnings in a prominent way and on the main panels if outer carton, if feasible.

3.3. Summary of product characteristics (SmPC), package leaflet (PIL) and labelling

The information which should be included on the labelling and package leaflet is provided in Title V of Directive 2001/83/EC. To minimise the risk of medication errors all new marketing authorisation applications for insulin products within the scope of this guidance (chapter 1) should include **as a minimum** the safety information outlined in table 3 in the SmPC and PIL respectively. References to relevant SmPC sections should be included in the EU Risk Management Plan, Part V Risk Minimisation Measures for each medication error.

Table 3: Medication error related safety information in the product information of **high-strength/fixed-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	SmPC section 4.4 and PIL section 2 under 'Warnings and precautions' and section 3 <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 standard 100 units/ml and higher units/ml strength insulin products, including by visually impaired or colour blind patients with diabetes mellitus	SmPC section 4.2 and PIL section 3 <ul style="list-style-type: none"> Explain that the product is available in two [or more] different strengths and no dose re-calculation is required. SmPC section 4.4 and PIL section 2 under 'Warnings and precautions' and section 3 <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 two [or more] strengths of insulins. SmPC section 6.6 and PIL section 3 <ul style="list-style-type: none"> Explain how the strength is highlighted on the product packaging.
Medication error due to non-compliance with	SmPC section 4.2 and PIL section 3 <ul style="list-style-type: none"> Explain that the pre-filled pen has been specifically designed for the

Medication error	Routine risk minimisation in SmPC and PIL
instructions for use: unnecessary dose recalculation	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 between standard and higher 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. <p>Labelling outer carton section 7 and label of the pre-filled pen device section 6 (if feasible)</p> <ul style="list-style-type: none"> To state that the insulin should only be used in the 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	<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</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 between conventional insulin and 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 product and mono injectable blood glucose lowering product. Explain how the dose counter on the pre-filled pen shows the number of units of insulin.

3.4. Regulatory requirements for user consultation

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

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

3.5. Pre-filled pen device usability testing

Marketing authorisation holders and applicants may consider relevant ISO standards such as IEC62366 which specifies a process for manufacturers to analyse, specify, develop and evaluate the usability of medical devices in relation to safety and ISO 14971 to identify the hazards associated with medical devices and to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls.

4. Additional risk minimisation measures

To minimise the risk of medication errors associated with high-strength and fixed-combination insulin products, marketing authorisation holders and applicants should adequately address the potential medication errors described in table 1 with routine risk minimisation measures and ensure that all options towards optimising the product design, naming, packaging and labelling in SmPC and PIL to prevent medication errors have been sufficiently explored in line with the recommendations in chapter 3. In addition, safety communication targeted to healthcare professionals, patients and carers using high-strength insulin and fixed-combination insulin products may be made publicly available (see chapter 5).

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

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

Marketing authorisation holders and applicants should follow the provisions of GVP Module XVI on risk minimisation measures: selection of tools and effectiveness indicators (Rev 1) and include appropriate effectiveness measures in the EU Risk Management Plan. This may include any risk minimisation measures implemented by drug product design or other protective measures based on user testing results referred to in chapter 3.4.

4.1. Conditions or restrictions with regard to the safe and effective use

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

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

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

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

- Healthcare Professional educational material

The Healthcare Professional educational material should contain the following elements:

- The Summary of Product Characteristics (SmPC)
- The Healthcare Professional guide
- The Patient guide

The Healthcare Professional guide shall contain the following key messages:

- The need to provide patients with the patient guide prior to prescribing or dispensing <PRODUCT NAME>.
- <[List key messages for healthcare professionals of chapter 5 for safety concerns as applicable]>
- <>

The Patient guide shall contain the following key messages:

- <[List key messages for patients of chapter 5 for safety concerns as applicable]>
- <>

4.2. Effectiveness measures

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

5. Safety communication published by the Agency

Complementary to product-specific routine risk minimisation measures described in chapter 3 the European Medicines Agency and EU national competent authorities may publish safety communication for healthcare professionals, patients and carers taking into account specific aspects relevant to national health care systems. The following safety communication is a suggestion based on the safety

concerns listed in table 1 and highlights the key recommendations for high-strength and fixed-combination insulin products users should adhere to.

5.1. Guidance on prevention of medication errors with high-strength insulins

A high-strength insulin is a medicine that contains insulin at a concentration of more than the standard 100 units/ml, which for many years has been the only strength available across the EU. The new high-strength medicines may allow patients to receive their dose in a single injection, and help meet an increasing need for higher doses of insulin. However, there are differences in the way these products are used compared with existing formulations and there is therefore a risk of medication errors if not used as recommended. There is also a potential risk of accidental mix-ups with existing insulin formulations of standard strength.

Patients and healthcare professionals are therefore advised to take extra care when using these medicines and to carefully follow the recommendations given below.

Recommendations for patients and carers

- If the concentration of insulin stated on your medicine pack is **higher than 100 units/ml**, you are using a high-strength insulin. Read the instructions in your package leaflet carefully before using this medicine.
- If you are using other types of insulin alongside your high-strength insulin, always check the packaging and the label of each type of insulin before every injection to avoid mixing them up.
- The high-strength insulin is supplied in a pre-filled pen and it should only be used with this device. The dose counter of the pen device displays the number of units of insulin irrespective of strength.
- If you are being transferred from a standard strength insulin you will usually be using the same number of units that you were when using the standard strength insulin⁷. This also applies if you are being transferred from a high strength to a standard strength insulin. Always follow the instructions of your healthcare professional.
- Your healthcare professional will highlight any differences in design between your high-strength insulin device and other standard strength insulin devices, especially if you have been transferred from a standard strength insulin to a high-strength insulin.
- You must never use a syringe to withdraw insulin from a pre-filled pen otherwise severe overdose may result.
- During the switch to a high-strength insulin and in the weeks after the switch you should measure your blood sugar levels more frequently.
- If you have any questions speak to your healthcare professional.

Recommendations for healthcare professionals

- Ensure that your patients and their carers are adequately informed on how to use their high-strength insulin.

⁷ In exceptional cases your dose may need to be changed because of differences in the way the high-strength and standard strength solutions are taken up into the body – your doctor will advise you if this is needed.

- The insulin is supplied in a pre-filled pen and it should only be used with this device. Healthcare professionals must never use a syringe to withdraw insulin from a pre-filled pen otherwise severe overdose can result.
- When switching patients from a low-strength insulin to an insulin formulation that is **not bioequivalent** (such as Toujeo, insulin glargine 300 units/ml), switching can be done on a unit to unit basis, but the dose may need to be adjusted to achieve target ranges for plasma glucose level. More detailed information on such dose adjustment is provided in the product information.
- Tell patients to closely monitor their blood sugar levels when starting a high-strength insulin and in the weeks after.
- Always prescribe the insulin dose in units (“units” to be spelled out and stated in lower case) and include the dose frequency. The strength of the insulin formulation should also be always included in the prescription.
- Explain differences in the design of the package and the prefilled pen device for high-strength insulins and standard strength insulins, especially if the patient has been transferred from a standard strength insulin to a high-strength insulin. Focus on colour differentiation, warning statements on carton/label and other safety design features (such as tactile elements on the prefilled pen).
- If different short-and long-acting insulins are being prescribed together, the differences in appearance and use between the two pen devices must be highlighted.
- Pharmacists should be aware that insulins are now available in different strengths.
- Pharmacists are encouraged to check that patients and carers are able to read the strength of insulin and the dose counter of the pen device before dispensing the medicine. Pharmacists should also check that patients have been trained on how to use the new pen.
- Patients who are blind or with poor vision must be instructed to always get assistance from another person who has good vision and is trained in using the insulin pen device.

In addition, healthcare professionals are encouraged to take the following precautions when storing and dispensing high-strength insulins:

- Ensure that electronic and paper systems used to prescribe and dispense these medicines facilitate the selection of any high-strength insulin.
- Carefully check the product strength selected in electronic prescribing or dispensing systems.
- Ensure that storage arrangements for high-strength insulins facilitate correct selection of the medicine and avoid confusion with other medicines.

5.2. Guidance on prevention of medication errors with diabetes medicines containing insulin and a non-insulin active substance

Recently, diabetes medicines that contain insulin in combination with a non-insulin active substance have been approved in the EU. These types of combination medicines are advantageous to patients since they reduce the number of injections they need to have and may help them keep to their treatment. However, there is a potential risk of patients receiving too little or too much of their medicine because of confusion that may arise over the way the doses are expressed for the individual components – the dose of the insulin is expressed in units while the dose of the non-insulin medicine may be expressed in other units such as mg.

Patients and healthcare professionals are therefore advised to take extra care when using these medicines and carefully follow the recommendations given below.

Recommendations for patients and carers

- Read the instructions in your package leaflet carefully before using your medicine.
- One dose step contains a set number of units of insulin plus a fixed amount of the non-insulin medicine. Before you use your medicine be clear on how many dose steps you require. Your healthcare professional will give you this information.
- Your healthcare professional will explain the design and features of your pen, including how the dose counter of the pen device shows the number of dose steps to be injected.
- During the switch to this type of combination medicine and in the weeks after the switch you should measure your blood sugar levels more frequently.
- If you have any questions about your treatment speak to your healthcare professional.

Recommendations for healthcare professionals

- Ensure that your patients and their carers are adequately informed on how to use their medicine.
- Explain to your patient that the dose counter of the pen device shows the number of dose steps to be injected. Always prescribe the dose of insulin and the dose of non-insulin to be injected as well as the dose frequency.
- If the patient has been transferred from another pen device, highlight the differences in design between the two devices.
- Pharmacists are encouraged to check that patients and carers are able to read the dose counter of the pen device before dispensing the medicine. Pharmacists should also check that patients have been trained on how to use the new pen.
- Patients who are blind or with poor vision must be instructed to always get assistance from another person who has good vision and is trained in using the insulin pen device.
- Tell patients to closely monitor their blood sugar levels when starting a medicine containing insulin and a non-insulin active substance and in the weeks after.

In addition, healthcare professionals are encouraged to take the following precautions when storing, prescribing and dispensing diabetes medicines that contain insulin in combination with a non-insulin active substance:

- Ensure that electronic and paper systems used to prescribe and dispense these medicines facilitate the selection of medicines containing insulin and a non-insulin active substance.
- Carefully check the product selected in electronic prescribing or dispensing systems.
- Ensure that storage arrangements for combination insulin medicines facilitate correct selection of the medicine and avoid confusion with other medicines.

6. Recommendations for clinical management and storage

Healthcare professionals are encouraged to

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

7. List of acronyms

CHMP	Committee for Human Medicinal Products
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
GVP	Good Pharmacovigilance Practice
HCP	Healthcare professional
ISMP	Institute for Safe Medication Practices
ISO	International Organisation for Standardisation
MAH	Marketing authorisation holder
ME	Medication error
NCA	National competent authority
NRG	Name Review Group
PIL	Package leaflet (patient information leaflet)
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk management plan
SmPC	Summary of product characteristics