Consent document

GUIDELINES FOR CORRECT INJECTION TECHNIQUE AND FOR PREVENTION OF LIPODYSTROPHY AND THE RISK OF ACCIDENTAL PUNCTURES

AMD-OSDI-SID Worksheet

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Presentation

In 2014 ISTAT data indicated that in Italy today there are around 3 million people with diabetes (1), with a varying regional distribution, greater in the southern regions. Furthermore the percentage of people with diabetes that require insulin therapy is significant because the incidence of Type 1 diabetes is 5.1%, while 26.7% of people with Type 2 diabetes give themselves one or more injections of insulin daily (2). The figures from the 2011 ARNO report show how during the last decade there was a progressive increase of the use of more modern insulin compounds, with a more physiological pharmacokinetics profile such as the rapid and basal analogues, and also the more modern therapeutic schemes (3).

Against this progress and general improvement of the quality of care, the 2012 AMD figures (3) show how only 22.2% of type 1 diabetics and 43.8% of type 2 diabetics achieve the recommended HbA1c targets and, conversely, how 25.7% of type 2 diabetics have values greater than 9% (2).

The reasons for failing to reach the optimum glycaemic index depend on a number of factors, including methods of administration, conservation and manipulation of the insulin, which all play an important role in treatment. Therefore, one of the aims of the treating team must be to acquire the knowledge and skills for correct use of injected hypoglycaemic drugs, informed selection and correct use of the devices for injecting them by the diabetics and their caregivers, to maximise their therapeutic potential.

The drafting of this consent document, which collates all scientific evidence available on this issue (including non-independent studies), organised according to hierarchical criteria, arose from these needs. The text underlines the fundamental role of structured, informed action, aimed at acquiring the knowledge and skills necessary for informed self-management of the disease (4).

The criterion for attributing the Quality level and the Strength of the guidance has been adopted from AMD-SID 2014 standards of care (5).

1. A correct injection technique is essential for optimising the action of the insulin and the other injectable diabetes treatment drugs.
   Correct injection technique involves the selection of the needle, rotation of injection sites, handling and storage of the insulin, the procedure by which the needle is injected into the skin, the duration of the injection with the use of pens, and manipulation of the skin before and after the injection.
   (Quality level III, Strength of guidance B)
2. The insulin must be injected into integral subcutaneous tissue, avoiding intramuscular injection which instead leads to faster absorption and potential risk of hypoglycaemia.
   (Quality level II, Strength of guidance B)
3. The activity of the insulin is not influenced by the depth it is injected into the subcutaneous tissue.

(Quality level V, Strength of guidance B)

4. The choice of needle length is crucial for guaranteeing optimum absorption of the insulin.
(Quality level III, Strength of guidance B)

5. Injections using a 4 mm x 32G needle cause patients minor pain and discomfort, leading to improved acceptability and compliance with the therapy.
(Quality level II, Strength of guidance A)

6. Injection with a pen and the use of a 4 mm x 32G needle ensures optimal absorption in all insulin therapy patients, including obese patients, is easier to perform and teach and, in the majority of cases does not require the pinch technique (or pinch-up), causes less anxiety and pain, leading to improved treatment acceptance and compliance.
(Quality level II, Strength of guidance A)

7. In paediatric age the safest needle for all children is 4 mm x 32G, in order to minimise unintended intramuscular injections, which can cause glycaemia variability phenomena. However in children in the 2-6 years age group, the 4 mm x 32G needle should be used with the pinch technique.
(Quality level II, Strength of guidance A)

8. Rapid action analogues and basal analogues can be injected at any site, because their absorption is not site-dependent. However, injecting regular human insulin is preferable on the abdominal skin because absorption is faster and more constant at this site.
(Quality level I, Strength of guidance A)

9. Rotation of injection sites over larger areas, not reusing the same needle multiple times, the pinch technique and angling the needle at 45° to the skin – if using needles greater than 4 mm – are essential factors for avoiding skin lesions and/or guaranteeing optimal insulin absorption.
(Quality level I, Strength of guidance A)

10. An effective, proven rotation scheme involves dividing the injection site into quadrants, injecting with a distance of at least 1 cm between one injection and another within each quadrant, in order to avoid repeat trauma at the same site.
(Quality level I, Strength of guidance A)

11. Failing to rotate the injection sites, using the same needle multiple times can lead to the formation of areas of lipodystrophy.
(Quality level III, Strength of guidance B)

12. The injection of insulin into lipodystrophic areas changes its pharmacokinetics and pharmacodynamics, leading to variable and unpredictable absorption and influencing the glycaemia compensation.
(Quality level II, Strength of guidance B)

13. When changing the injection site from a lipodystrophic to a healthy area, the doses of insulin should be monitored and/or reduced because absorption will be improved. Reducing the insulin dose varies from individual to individual and must be accompanied by increased glycaemia self-monitoring.
(Quality level II, Strength of guidance A)

14. Appropriate training by the treatment *team* is necessary for all persons with diabetes starting injection therapy, and must be repeated over time.
(Quality level II, Strength of guidance A)

15. The injection sites of all diabetic patients undergoing injection therapy should be inspected and palpated regularly at each visit. Education on the correct injection technique should be systematically reinforced. Patients should be taught and it should be confirmed that they

know how to self-palpate the injection sites.
(Quality level II, Strength of guidance B)

16. Insulin injections carried out using a syringe should always be performed using the pinch technique at any body site because at the moment there are no syringe needles shorter than 8 mm and the risk of intramuscular injection is therefore elevated.
(Quality level II, Strength of guidance B)

17. Nursing staff must be trained on the correct injection techniques both for pens and syringes.
(Quality level II, Strength of guidance B)

18. According to the 2010 European Directive and the associated norms adopted in the member states, all injection practices or other actions performed for diabetes management by medical staff in care environments (hospitals, emergency areas, clinics, ambulances etc) should be performed solely using safety devices, to minimise the risk of accidental puncture and to provide health protection for the operators, patients and their families at all stages of use, until disposal of the sharps.
(Quality level I, Strength of guidance A)

19. Domiciliary use of safety needles or syringes is also prescribed for special populations of diabetics carrying AIDS, HBV and HCV.
(Quality level II, Strength of guidance B)

20. In all medical environments where insulin pens are used, rigourous procedures must be followed according to which each insulin pen must correspond to a particular patient, to avoid risking transmission of infections between the various patients through the use of the same pre-filled pen.
(Quality level I, Strength of guidance A)

21. Storage of insulin in hospital and at home (pens and vials) must follow the manufacturer's indications set out in the datasheets approved by AIFA. Patients must be trained on these indications.
(Quality level II, Strength of guidance B)

Comment

To ensure that the activity of insulin injected into diabetic patients meets the expected pharmacokinetics and pharmacodynamics profiles, the injection technique must be correct (6-9), while avoiding errors that would change its activity (10,11). As insulin administration is a daily activity, there is the risk that without suitable training support the diabetic patient may carry out a superficial and often incorrect delivery, thereby contributing to increased glycaemia variability (10).

For optimum absorption the insulin must be injected into the subcutaneous tissue and not into the dermis or the muscle, therefore the choice of needle length is crucial. Needles in syringes are longer than in pens and when choosing between syringes and pens diabetic people prefer pens, even if it has been shown that by using the correct injection technique the efficacy and safety of the two systems are comparable, with similar glycaemia control and risk of complications (12,13).

The skin has an average thickness of 2.23 mm in the arms, 1.87 in the thighs, 2.15 in the abdomen and 2.41 in the glutei, in adult patients with diabetes (14). In paediatric age the thickness of the skin varies from 1.58 mm in the arm of a child to 2.29 mm in the glutei of an adolescent (15).

Accidental intramuscular injection frequently causes hypoglycaemia (16-20). The use of a 4 mm x 32G perpendicular needle without pinching minimises the risk of intramuscular injection, without increasing the flow of insulin from the injection site (21,22,23). The use of a 4 mm x 32G needle is suitable for all insulin therapy patients, including obese patients, regardless of BMI (21,24,25). The pinch technique could however be necessary in particularly slim patients

(8,15,23,26,27,). When transitioning from a longer needle to a shorter one there could be changes in the absorption of insulin for which an intensification of glycaemia monitoring is recommended (27,28).

The subcutis has a thickness which varies significantly according to gender, area of the body, body mass index, age, ethnicity, morphology of the individual patient with diabetes and position within the area selected for injection (14,16). The estimated risk of intramuscular injection is 15.3% with needles of 8 mm, 5.7% with needles of 6 mm and 0.4% with needles of 4 mm (14).

Rotation of the injection sites over a larger area, not reusing the same needle multiple times, the pinch technique and angling the needle at 45° to the skin – if using needles longer than 4 mm – are essential factors for avoiding skin lesions and ensuring optimum absorption of the insulin (11,29-35).

The better pharmacokinetics of insulin analogues has enabled reducing glycaemia variability in the same person and among groups of diabetics, making patient management simpler (35). In spite of this technological progress, certain variability factors in the absorption are still able to influence the insulin activity: physical exercise, elevated insulin dose, failure to wait 10 seconds at the end of the injection and before removing the needle from the skin (after the piston of the pen has reached the end), use of mixtures requiring the correct mixing technique (34,35). Another example of how the injection technique can influence insulin pharmacokinetics and how an intramuscular injection can create unexpected hypoglycaemia, is provided by insulin glargine (36), which bases its long duration of action on its ability to precipitate in the subcutaneous skin at neutral pH. When injected in the muscle tissue or in the circulation it could lose this characteristic and acquire biological activity comparable to that of rapid insulin (37) and therefore potentially cause unexpected hypoglycaemia episodes (35) within a few hours following administration. With insulin detemir the same care must be taken to avoid administration into the muscle or into the circulation, as it is soluble and therefore can acquire a fast biological activity, although initially slowed down by binding to albumin (38-40). There are no data yet available regarding the more recently marketed delayed action insulin degludec.

It has been shown that the absorption of insulin does not change whatever the depth it is injected into the subcutis (41-45), moreover the use of specific injection sites by type of insulin compound is valid only for human insulins (6-8). In this latter case, it is recommended to use the same anatomical region for injections at the same time of day, injecting the insulin with a sequence of punctures at a regular distance of at least 1 cm between them within each region, in order to avoid repetition traumas at the same point. For human insulin the abdomen is the best site for injections linked to meals (27).

The choice of device for delivering the insulin, in particular the length of the needle, has been found to be a factor that can affect the correct absorption of the drug, whether a pen or syringe is used. Syringes are marketed in Italy for delivering insulin with needles less than 8 mm and their use increases the risk of intramuscular injections if the correct pinch and/or angling of the needle at 45° to the skin is not carried out (8,20,31). For this reason the use of pens with a 4 mm x 32G needle is preferred to minimise the risk of intramuscular injection. The diameter (G) and the grinding of the needle are important factors for patients' acceptability and choice (21,22,41-44,46-48). Insulin injected with a 4 mm x 32G needle and with the appropriate grinding cause less pain and discomfort and is preferred by patients, giving them equivalent glycaemia control to 5 mm x 31G and 8 mm x 31G mm needles, whether in obese or non-obese patients and has greater acceptance and compliance (42,48,49).

One of the more common complications in insulin injection therapy is the development of lipodystrophy, which is also possible with continual insulin infusion systems (11,50-51,53). The exact aetiology is not entirely clear, even if various causal factors have been proposed, such as repeated injection trauma in highly used areas, needle reuse, high dosages of insulin that could act

on the adipose tissue as growth factor (30,54). Among patients that reuse needles, 70% develop lipodystrophies, 84% for DM1 patients (11).

Lipodystrophies are very widespread: Vardar and Kizilci (53) report a prevalence of 48.8% in a population of 215 Turkish subjects undergoing insulin therapy for at least 2 years; for Hauner et al. (55) the prevalence was 28.7% in 233 patients with type 1 diabetes. More recently Blanco et al. (11) documented that 64.4% of patients investigated presented lipodystrophies, with a strong relationship with inadequate rotation of sites. Moreover 39.1% of patients with lipohypertrophy demonstrated unexplainable hypoglycaemias and 49.1% had wide glycaemic variability. Various studies have shown that absorption of injected insulin in lipodystrophic areas can be delayed or become unpredictable (56-59), representing a potential factor for the deterioration of glycaemic compensation (59-67). Correct rotation of sites is a critical factor in the prevention of lipodystrophies: it reduces glycaemia variability, the risk of hypoglycaemia and the consumption of insulin (11). It is important to diagnose lipodystrophies, educate the patient with simple and practical rules on how to prevent them: use larger surface areas for the injection, rotate between and within sites, do not reuse the pen or syringe needle (8,11,26,65). As the risk of intramuscular injections with a 4 mm x 32G needle is lower than with longer needles, the use of this needle permits a safer injection at all injection sites, in larger areas ensuring better rotation of sites (14).

The recommendation for strictly individual use (68,69) for pens is associated with the documented aspiration of biological material in the insulin container of the pen (70,71), when the pressure on the piston is released at the end of the injection, causing an aspiration mechanism. The quantity of biological material aspirated forms a different risk independent from reusing the same needle and it is more than sufficient for the transmission of the more than 20 pathogens, among which the most frequent are HCV, HBV and HIV (72-76). The Food and Drug Administration (FDA) issued some alerts against the administration of insulin to multiple people using the same pen (75,76).

To enable traceability, all pens in use at health facilities must be catalogued and inventorised by the pharmacist before the medical personnel who use them. Each pen in use at healthcare facilities must also be labelled with the intended patient's details and must bear indication of the start date of use and the expiry date indicated by the manufacturer and must be stored using appropriate methods (as for all other drugs in use) by the department staff and not by the patient (77-80).

The use of sharps (needles and fingerpricks) is a role only for medical personnel and non-critical patients who are expert in insulin self-administration and glycaemia control, their direct use is permitted, with agreement with the team on the methods, also defining the correct disposal methods for the material used (81-83).

Correct practices for minimising the risk impose the use of pen and syringe needles fitted with safety devices and come not only from scientific literature (84-86) but especially from the legislative regulations on safety.

The standard ISO 23908 (87), other regulatory provisions and the recent Cochrane Collaboration Initiative (88,89), define the characteristics necessary to describe the safety devices (Table 1). Safety must be guaranteed both for the patient (point of the needle), and for insertion into the cartridge. In actual fact it has been calculated that around 10% of accidental punctures with pen needles take place from the cartridge part (90,91).

Safety device definition[1]

- **According to Italian law and international standards (105), the safety device must be able to protect the hands of the operator during and at the end of the procedure for which the device itself is used and for assuring permanent protection during collection and the final disposal.**

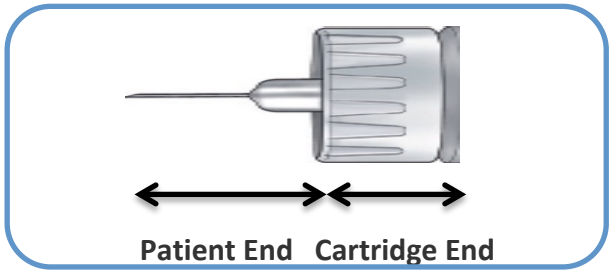
(ISO 23908:2011; 4.1.2)
• **Both ends of the needle must be protected. (ISO 23908:2011; 4.1.2)** 
• **The operator must be able to activate the protection mechanism in automatic mode (active or passive trigger) and using a single hand.** **(ISO 23908:2011; 4.1.1- 4.1.4- 4.2)**
• **The operator's hands must always be able to be behind the shielded part of the device.** **(ISO 23908:2011; 4.1.4)**
• **The protection mechanism must be as readily activated as possible.** **(ISO 23908:2011; 4.2)**
• **The device must be reliable, easy to use and intuitive.** **(ISO 23908:2011; 4.1.3)**
• **The protection mechanism must create an effective, permanent and irreversible barrier between the shielded part of the device and the operator.** **(ISO 23908:2011; 4.3)**
• **The protection mechanism may not be disabled and must ensure protection even during and after disposal.** **(ISO 23908:2011; 4.1.2-5.3.2)**
• **The device must have an (audible and/or visible) signal that enables confirming activation of the protection mechanism.** **(ISO 23908:2011; 4.1.3)**
• **Using the device must not generate additional safety risks (e.g. risk of mucocutaneous exposure).** **(ISO 23908:2011; 4.1.5)**
• **The device must not compromise the quality of the intervention and the patient's safety in anyway.** **(ISO 23908:2011; 4.1.5)**

Table 1. Definitions and references to the ISO standard for safety devices

Aspiration of insulin using syringes from preloaded pens is not recommended by manufacturers as there are no trials that indicate this practice can guarantee removal of the correct doses of insulin and because the two injection systems have been designed for a use different from this procedure, as specified in the technical specifications. This practice is permitted only in the case of emergency or failure of the pen to function (92-94). Note that drawing insulin from a cartridge or from a pen using a syringe causes the formation of air bubbles, which can cause an error in drawing the subsequent dose if the pen is reused, with obvious clinical repercussions. The recommendation not to draw insulin from the pen cartridge, unless in an emergency, derives from the product technical specifications approved by the AIFA and from an alert of the Canadian Institute of Safe Medication Practices in 2008 (91).

Education

Insulin therapy is a daily and enduring treatment, for which there is the risk that the person with diabetes – without suitable and constant education – may over time practice it more and more informally and often incorrectly, thereby increasing glycaemia variability with the consequent risk of deterioration of the glycaemia control (10).

The importance of adequate training on injection techniques by healthcare operators is obvious, however it has been shown that training is often lacking (9), which is confirmed by the frequency of skin lesions due to incorrect injection technique (11,34,53,55,63).

The medical team must empower the person with diabetes, making them capable of making daily decisions closely related to the therapy. Specifically, self-administration of insulin requires the skills necessary to guarantee the injection is performed using the correct technique (95-97).

The patient must understand that there is a relationship between appropriate injection technique and good glycaemia control (97-99), that alterations of the pharmacokinetics of insulin following incorrect injection technique and the consequent risk that these alterations may cause the onset or accelerate complications of diabetes (10,11,14,29).

All patients that start injection therapy for the treatment of diabetes must be adequately trained on correct injection techniques and the training must not be limited to the start of therapy but be continual, with regular updating throughout the subsequent follow-up (8,21,26,61-63,100). The training must be periodically reinforced and the medical staff must also periodically and systematically inspect and palpate the injection sites in all diabetic patients undergoing injection therapy (8,22,85,99-102), especially where there are unexplained hypoglycaemia episodes (11). The training must emphasise the negative consequences of intramuscular injections of insulin or in areas of lipodystrophy and must train the person with diabetes to recognise lipodystrophy (77,100-104).

The person with diabetes must be taught that the frequency of glycaemia self-control should be intensified when passing from using longer to shorter needles and when moving on to healthy areas of skin from lipodystrophic areas (8-11,59,60).

Educating patients on self-management of diabetes in hospital is a difficult and demanding role (105-109).

During admission is not the most appropriate time to run a training programme on diabetes. However, a training intervention on certain essential aspects, such as the methods for injecting insulin and the principles of self-control, must be provided before discharge (109).

Hospitalised patients are suffering, stressed and also in an environment that is not the most ideal for learning. During the admission however it is necessary to provide basic education, with information sufficient to render the patient capable of not running risks on returning home. People with a new diagnosis of diabetes and those who have started insulin treatment or glycaemia self-control must be trained in order to guarantee safe management in a non-hospital environment and introduced to the diabetology service on discharge for scheduling regular follow-ups (109). The role of educational therapy in hospitalised people with diabetes has been the subject of a recent publication (106) which observed how the re-hospitalisation rate at 30 days is reduced in a statistically significant way in patients who have received educational therapy and this figure remained significant even after correction for sociodemographic factors and for related disease factors.

Medical staff must be trained on the use of the various devices for injecting insulin, including needles and safety syringes, the correct injection techniques and to adopt all procedures necessary for minimising the risk of accidental puncture (77,110-112).

Addendum: Recommendation on injection sites of basal insulin

Clinical studies confirm that there is no clinically significant difference in the absorption of glargine insulin whether injected in the abdomen, deltoid region or the thigh (113). Subcutaneous injection of glargine in the deltoid region, thigh or abdomen of healthy volunteers did not cause variation in the absorption and bioavailability, in fact T75% statistical comparisons and residual radioactivity 24 hours after administration showed no significant difference of absorption between the various injection sites (114).

Indications provided by the EMA and the manufacturer's datasheet for detemir clearly indicate that this insulin preparation may be administered via subcutaneous injection in the abdominal wall, the thighs, the upper part of the arm, shoulders or buttocks (115), and recommend always using the same site if possible and not preferring one in particular (116). In actual fact, the absolute bioavailability is 64, 59, and 65% after subcutaneous administration in the abdomen, thigh and deltoid respectively; AUCinf, AUC0-5h and Cmax are significantly higher (approximately 10%, 35% and 20% respectively) after subcutaneous injection in the abdomen or deltoid, compared to the thigh. The differences observed indicate that, as for other insulin preparations, subjects treated with detemir insulin must be advised to rotate the injection sites within the same area of the body (116).

Recent pharmacokinetic data on degludec insulin allow all injection sites to be used regardless, because there are no site-dependent differences in absorption and bioavailability (117).

Conflict of interest: none*

This document was drafted entirely independently with finance external to the three Scientific Associations AMD, OSDI, SID

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116. SCIENTIFIC DISCUSSION This module reflects the initial scientific discussion for the approval of Levemir. For information on changes after approval please refer to module 8.

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