

Insulin Icodec: A Pharmacological Innovation That Enables Once-Weekly Insulin Therapy

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ABSTRACT:

Icodec is the first long-acting basal insulin analogue formulated for the management of diabetes mellitus; this represents a major advancement in insulin therapy. This long-acting basal insulin is engineered with strong but reversible albumin binding and enhanced molecular stability, allowing an effective half-life of about seven days and maintaining sustained insulin activity throughout the week. Clinical evidence from the last stage study trials has indicated that once-weekly administered insulin provides glycaemic regulation similar to or better than daily administered basal insulins, with significant improvements in glycated haemoglobin (HbA1c) and high patient satisfaction. This long-acting insulin has the potential to improve the compliance of patients during treatment as it reduces the frequency of injections from about 356 to around 52 injections per year. This potentially also increases the persistence and quality of life of diabetic patients. Although careful dose titration is required during initiation of decrease the potential for hypoglycaemia, its overall safety profile is similar to that of conventional basal insulins. This innovative therapy marks a significant step toward simplifying diabetes management and improving long-term clinical outcomes for both patients and health care providers.

KEY WORDS : Insulin icodec , weekly administered basal insulin, Type 2 diabetes mellitus, Glycated haemoglobin (HbA1c), Albumin binding, Glycaemic control.

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INTRODUCTION :

Diabetes is a highly frequent prolonged metabolic abnormality that currently affects over 500 million patients worldwide. The international diabetes federation (IDF) prognosticates that this figure is subject to increase upto 643 million by the year 2030. (1)

This disease is recognized by a constant hyperglycaemia condition, that is associated with type 2 diabetes, being the major category, comprising nearly 90% cases of all diabetes. The elevated blood glucose level is predominantly induced by reduced insulin sensitivity and gradual dysfunction of the beta cells of pancreas. Diabetes (type 2) is a prolonged disorder identified via advanced degradation of insulin therapy, causing

damage to the beta cells of pancreas, that results in deteriorating hyperglycaemia over a period of time. Long-term deterioration inhibits continuous glycaemic control containing controlled potent diabetes.(2)

Insulin medication is usually implemented in patients suffering from type 2 diabetes, the desired glycaemic target levels are not obtained by the other diabetic medications as they maybe not suitable to the patient or metabolic decomposition due to hyperglycemia. (3)

Basal insulin therapy is a key component in management of type 1 diabetes conditions as the disease enhances. Icodec (NM1436) is a primary treatment for type 1 diabetes condition, that involves regular administration of basal insulin and prandial

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insulin therapy or regular infusion administration via insulin infusion device.(3)

Icodec which is ultra long-acting basal insulin analogue is a new weekly administered basal insulin which binds effectively but temporarily to serum albumin. Its persistent duration of action is mainly because of development of a primarily unbound albumin, due to which it steadily liberates the effective Icodec and is the major cause of its prolonged activity. Icodec has received approval from health authorities of Canada for Weekly dosage regimen to be used in individuals effected with diabetes to enhance patient outcomes. Icodec is a prolonged acting insulin which may introduced via subcutaneous injection every week, unlike currently available once-daily prolonged acting basal insulin. Like other insulin, the administration of insulin icodec is personalised and adjusted based on the patients' needs to meet their glycaemic control targets, this makes it a personalised treatment.(4)

Across the past 25 consecutive years, prolonged acting daily basal insulin analogue had advanced treatment effectiveness and Clinical safety relative to previous insulin preparations. A weekly insulin with a balanced pharmacokinetic pattern may decrease that injection strain and reduce glycaemic fluctuations, hence leading to improved treatment compliance and continuation of insulin therapy.(5)

Since insulin was discovered in 1921, insulin therapy has been related with at least two significant drawbacks, despite significant advancement in insulin composition during the last century. The insulin treatment has an injectable form of delivery and is linked to impulsive hypoglycaemia. Comparable positive effects are anticipated from weekly administered insulin therapy, if it is well-tolerated and efficient.(6)

Renal dysfunction is a frequent chronic condition in diabetes, as up to 40% of diabetes patients have an arising persistent renal disorder. Icodec is an emerging ultra long-acting insulin analogue under development to offer basal insulin, extent when infused weekly once. (7)

Although, the life sustaining impacts with unmatched glucose reduction effectiveness of insulin, overall glycaemic management in the Individuals With diabetes mellitus (type 1 and type 2) fails to attain establishment targets. (8)

REVIEW OF LITERATURE:

Clinical studies and phase 3 trials show that weekly administered insulin provides efficient glycaemic regulation similar to daily administered basal insulin, while substantially decreasing injection strain in patients with T2DM. Overview prioritises that transferring trials validation into practice includes careful dose injection, weekly titration, and ensure safe real-world use (3)

phase III randomized Clinical trials show that weekly administered insulin attains efficient glycaemic control analogue to once-daily basal insulin therapy in T2DM. Pooled analytical results also indicates a typically adequate safety profile with hypoglycaemia rates similar to standard insulin therapy. (2)

Systemic adaptations in insulin Icodec, particularly increased disulphide bond stability, sustain its half-life and support a once-weekly dosing profile. This pharmacokinetic progress provides continuous insulin action and more stable glycaemic control compared with established basal insulin composition.(9)

Studies show that different levels of renal or hepatic dysfunction have limited therapeutic relevant effect on the pharmacokinetic profile of weekly administered insulin icodec, supporting its continuous exposure across Individual population. (7)

Late phase study shows that diabetic individuals of Indian origin showed that once- weekly insulin icodec established efficient glycemic levels that had a favourable safety profile analogous to the standard basal insulin therapy(10)

PATHOPHYSIOLOGY:-

Diabetes mellitus is a metabolic disorder characterized by sustained hyperglycemia, which is caused by impaired insulin release (11).The World Health Organization (WHO) has developed several diabetes mellitus classification schemes, the most widely used of which are currently:Type 1 diabetes that is insulin dependent form of diabetes, type 2 diabetes which is the non insulin dependent form of diabetes and various particular forms of the disease, including gestational diabetes. (11)

TYPE 1 DIABETES MILLITUS (T1DM) :

Type 1 diabetes which is insulin dependent form bought on due to lack of systemic insulin that arises due to the malfunctioning of pancreatic beta cell.(12)The hormone insulin is in charge of the metabolism of glucose .(13)The glucose levels in the

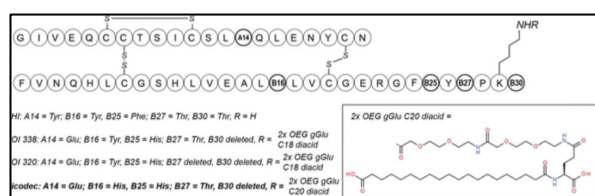
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blood are reduced by decreasing its synthesis by the liver and the amplifying absorption of glucose in the peripheral tissues comprising of the voluntary muscles and fatty tissues. Additionally, insulin promotes protein synthesis while inhibiting lipolysis and proteolysis.(13)

TYPE 2 DIABETES MILLITUS :

T2DM is defined by insulin resistance, a deteriorating pancreatic beta cells activity, and cells that are insensitive to signal transduction and mitochondrial depletion.(12).The first is that insulin's effect on peripheral tissues is diminished. The second is the malfunction of pancreatic beta cells, which manifests as the incapacity to generate enough insulin to counteract reduced insulin sensitivity in extra hepatic tissue. This is commonly referred to as insulin resistance. Due to beta cell malfunction, insulin production may eventually fall short of compensating for insulin resistance. (11)

STRUCTURE :



* **Fig1: Selected insulin analogs structures: insulin icodec.(14)**

The ultra-long acting oral basal insulin analogue OI338 was redesigned to create insulin icodec. In this redesigned analog, C18 fatty diacid side chain was replaced with C20 fatty diacid side chain as the fatty diacid. LysB29 has an ϵ -amino group which is linked to the C20 fatty diacid through a Gamma glutamyl residue spacer and a PEG-mimicking hydrophilic moiety, forming the human serum albumin (HSA)-binding acylation moiety. Additionally, the insulin analog contains four amino acid substitutions: A14E (TyrA14--->Glu), B16H (TyrB16--->His), B25H (PheB25--->His), and desB30 (deletion of ThrB30)(15). These structural modifications were designed to achieve four key molecular characteristics: strong albumin affinity, reduced insulin receptor affinity, enhanced molecular stability, and high aqueous solubility. (15) Collectively, these modifications promote reversible albumin binding and stable hexamer formation, resulting in sustained insulin release and an ultra-long duration of glucose-lowering action. (16)

STRUCTURE ACTIVITY RELATIONSHIP :-

The structural modifications introduced in insulin icodec were designed to optimize its pharmacokinetic properties. Replacement of the C18 fatty diacid side chain with a C20 fatty diacid side chain markedly increased reversible albumin binding, thereby reducing insulin clearance and extending plasma half-life. The specific amino acid substitutions including A14E, B16H and B25H decreased insulin receptor binding affinity, minimizing receptor-mediated clearance, while A14E and B25H also improved molecular solubility. In addition, these amino acid alterations enhances structural integrity by reducing enzyme mediated degradation. Collectively, these changes enables the design of weekly administered basal insulin analogue with extended duration of action.(15)

RECEPTOR OF INSULIN ICODEC:-

The metabolic activity of insulin is mediated by the Insulin Receptor (IR) which is the primary target of insulin icodec. During preclinical evaluation, the insulin receptor and insulin like growth factor -1 Receptor was also examined to assess receptor selectivity, safety and tolerability of ultra long acting insulin analogue.(15)

RECEPTOR CLASS :

Ultra long acting insulin analogue exerts its effects by interacting with the insulin receptor, a member of the Receptor tyrosine kinase (RTK). Interaction of insulin induces signalling receptor autophosphorylation, which initiates multiple intracellular signalling pathways responsible for regulating glucose metabolism and cellular growth. (17)

STRUCTURE :

The insulin receptor protein is a multi-subunit transmembrane glycoprotein ($\alpha_2\beta_2$) consisting of a pair of extracellular α subunits and two membrane spanning β subunits joined by disulfide linkage. The α -subunits contain the insulin binding sites, whereas the β -subunits possess intracellular tyrosine kinase domains that transmit the insulin signal into the cell. (19)

DISTRIBUTION :

Insulin receptors are widely distributed throughout the body, with the highest expression in the liver, skeletal muscle, and fat tissues. They are also found

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in the brain, kidneys, and several other tissues where they regulate metabolic homeostasis(17)

ENDOGENOUS LIGAND :

The endogenous ligand for the insulin receptor is human insulin, a peptide based endocrine messenger released from the pancreatic beta cells. Binding of insulin to the receptor initiates signalling pathways that regulate glucose uptake and overall energy metabolism. (17)

SIGNALLING PATHWAY :

Insulin receptor interaction activates receptor autophosphorylation and initiates downstream signalling pathways. Experimental studies demonstrated phosphorylation of the insulin receptor (IR) followed by stimulation of protein kinase B (AKT) phosphorylation and extracellular signal regulated kinase (ERK). These signalling pathways control cellular glucose uptake, glycogen formation, protein biosynthesis and cellular survival, indicating that insulin icodec preserves the normal biological signalling of native human insulin. (14)

ROLE IN PHYSIOLOGY:

Activation of the insulin receptor is essential for maintaining glucose homeostasis. It enhances glucose transport into skeletal muscle tissue and fat tissues, increases glycogen formation in the hepatic tissue, regulates lipid, protein metabolism and supports cellular growth, differentiation, and survival. (17)

INTERACTION WITH INSULIN ICODEC :

Insulin icodec retains selective interaction with human insulin receptor, while exhibiting markedly lowers binding strength towards the insulin-like growth factor-1 receptor (IGF-1R), demonstrating good receptor selectivity. Its strong reversible interaction with human serum albumin (HSA) reduces receptor-mediated clearance and prolongs plasma half-life. Despite its reduced receptor affinity, insulin icodec functions as a full agonist, effectively activating the insulin receptor and downstream signalling proteins AKT and ERK, while maintaining metabolic responses such as glycogen synthesis. These properties enable sustained glucose-lowering activity and support once-weekly administration without compromising receptor signalling. (18)

MECHANISM OF ACTION :

Ultra long-acting insulin analogue is an anabolic peptide hormone that is synthesized by the beta cells

of the pancreatic islets located in pancreas. Its pharmacological action varies based on its blood plasma concentrations. At a minimal level, insulin inhibits ketone and subsequently halts gluconeogenesis, which prevents an increase in glucose levels (19). As plasma concentrations rise, it facilitates glucose uptake by cells, promotes glycogen synthesis, and ultimately functions as an anabolic hormone. The presence of reduced insulin sensitivity can result in diminished insulin responsiveness changes in metabolic conditions, while a complete lack of insulin results in a catabolic state and encourages ketogenesis.(19)

INSULIN ICODEC (NN14436): -

Icodec is a weekly administered medication that has a prolonged plasma half-life of about one week and can boost compliance. Its extended duration of action is due to a fatty acid side chain. The ultra-long oral basal insulin was redesigned to create insulin icodec (20) It is a human insulin analogue that has three amino acid substitutions changes and an appended C20 dicarboxylic acid enables to albumin binding moiety reversibly (like insulin detemir),extending its plasma half-life of about 196 hours.(21) Icodec's strong, reversible human albumin binding, which prevents formation of subcutaneous depots, accounts for its prolonged activity .Icodec's half-life is further extended by three amino acid substitutions changes ,which lower insulin receptor binding affinity and elimination(21).An equivalent weekly administered dose of icodec is seven times the daily basal insulin dose ; one unit of icodec lowers blood sugar levels in the same way as one unit of an equivalent daily basal insulin analogue (21)

PHARMACOLOGICAL MANAGEMENT :

Insulin therapy continues to be a cornerstone of diabetes management (22).Individuals with diabetes frequently require insulin treatment to sustain and achieve glycaemic controlled levels. (10) Because their bodies are unable to create insulin, individuals with type 1 diabetes depend on daily injectable insulin therapy. The body either has insufficient insulin production or impaired insulin utilization(10).Injection site reactions and numerous daily injections are a significant annoyance for patients. (13)

Ultra long acting insulin analogue, a once-weekly subcutaneous administration, enhances the glycaemic control in individuals with T2DM(13).Once a week, the unique analog should

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be subcutaneously injected into the thigh, belly, and upper arm---sites that are typically used to give other insulin analogs. Prefilled pens of 1 mL, 0.5 mL and 3 mL, each containing a standard concentration of 700 IU/mL are among the three packaging options for icodec. (23) An equal weekly administered dose of icodec sevenfold of the corresponding dose of a daily basal insulin, and one unit of icodec lowers blood sugar levels in the same way as per unit of comparative daily administered basal insulins. (21). Every week, the Icodec dosage should be determined and modified. (23)

DOSE CALCULATION:

A Weekly administered basal insulin regimen may offer potential benefits, however there are a number of possible dosage issues. The current dosage schedules, which depend on once-daily basal insulin administration, would be significantly altered by these insulins. Weekly dose equivalents must be determined in order to start these insulins, both for patients who are new to insulin and for those who are transitioning from a once-daily to 0.4 U/kg/day would receive roughly 196 units per week, 28 units in daily equivalents. (5)

WARNINGS, PRECAUTIONS, CONTRAINDICATIONS:

Insulin icodec has the same cautions, warnings, and contraindications as any basal insulin medication. Concurrent use of insulin secretagogues and other insulin medications increases the risk of hypoglycaemia. Lack of meal and excessive exercise increase the risk of hypoglycaemia. Irritation at the injection site is also observed. Insulin Icodec should not be administered to patients who are allergic to or hypersensitive to any of its constituents. When taking insulin icodec, patients with hepatic or renal failure should check their blood sugar more regularly. (12)

RECENT ADVANCES

In recent studies of insulin Icodec, the main outcome of all 5 studies was variation in HbA1c (glycated haemoglobin) from the initial value to end of therapy.

Persistent glucose surveillance was employed in initial phase and late phase studies; it was utilised to evaluate duration within range (TIR; 70-180 mg/dL [3.9-10.0 mmol/L]), duration beyond the range (TAR; > 180 mg/dL [> 10.0 mmol/L]), and duration

under the range (TBR; < 54 mg/dL [< 3.0 mmol/L]) throughout constant 4-week duration. [6, 7, 9]

The effectiveness and therapeutic safety profiles of icodec in individuals diagnosed with diabetes was evidenced by "Phase IIIa ONWARDS 1-6 clinical program" which ultimately results in an official approval in European Union and other countries (3). In clinical studies the randomized control trials (RCT), and in addition to individual studies on patient with prior basal insulin therapy provide valuable evidence in investigating the future effectiveness and safety profiles associated with insulin icodec [NN1436]. (24)

Latest studies reveal that the insulin icodec has the possibility of being administered in the femoral region [thigh region], abdomen or proximal arm subcutaneously. This doesn't affect the drug exposure and also shows similar blood glucose - lowering effect, providing better convenience for patients. (25)

In people with prolonged history of type 2 diabetes treated with basal-bolus insulin therapy, icodec achieved similar effect to that of once daily glargine U100 (26)

CHALLENGES AND LIMITATIONS: ~

1- *Distribution challenges:* -

Natural insulin primarily enters liver in higher concentration, but basal insulin analogues is administered subcutaneously because of which natural hepatic-peripheral insulin gradient is not maintained appropriately and also liver fails to control glucose production effectively. Furthermore, strategies to promote an increase in liver specific insulinization with insulin preparation of human origin and modified insulin derivatives may be accompanied by many difficulties associated with excessive insulinization of peripheral body tissues, potentially increasing the risk of hypoglycemic events and weight gain.

2- *Pharmacokinetic variability:* -

In body different basal insulins absorb preferentially in varying proportions, because of which pharmacokinetics and pharmacodynamics profiles show variability. Notably these variations depend on injection site, physical form and half-life of insulin.

Insulin glargine U100 shows higher order of variability compared to insulin detemir and insulin degludec.

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Insulin with longer half-life shows reduced level of variables.

Variability in insulin absorption and its pharmacokinetics and pharmacodynamics parameters may affect glycaemic control, creating a challenge and also representing an important limitation in insulin icodec therapy.

3 -*Prolongation of Drug Action* Insulin icodec [NN1436] uses several innovative mechanisms to prolong the duration of its action, although it being advantageous this "Novel Mechanism" creates challenges. (5)

4- *Dose Adjustment Challenges:* -

Owing to its exceptionally prolonged half-life, it needs cautious dose titration.

Difficult to adjust dose during illness, surgery, or sudden changes in insulin requirement. Overdose of insulin remains active for long duration which increases the risk of prolonged. (13)

5- *Increased risk of hypoglycaemia:* - During the treatment of insulin icodec level 1 and level 2 hypoglycaemic events are more.

In some patients repeated episodes of hypoglycaemia were reported, which indicates few patients are more susceptible to blood glucose. Because of which, during the therapy of insulin icodec careful glucose monitoring and appropriate dose titration is necessary. (27)

FUTURE PERSPECTIVE: -

1- Improving personalized dosing strategies: - According to patients need insulin icodec dose is adapting more precisely. Future research mostly focuses on age, weight, lifestyle and blood glucose levels; accordingly, dose can be adjusted.

2- Evaluating sustained CVS and renal outcomes Assessing the long-time effect of icodec on CVS and renal outcomes. Research mainly focuses on whether the therapy decrease the complications of heart and kidney issues. (28)

CONCLUSION:

The Ultra long-acting analogue of basal insulin constitutes a significant progress in basal insulin treatment for T2DM, allowing weekly administration treatment possible for patients, which decreases the injection strain and may enhance patient adherence. Clinical research demonstrated glycaemic control similar, and certain cases with greater effectiveness than conventional daily

administered basal insulin analogues, while maintaining a favorable safety profile. (13)

The Ultra long-acting analogue of basal insulin provides cost saving potential relative to degludec in insulin native individuals with T2DM. However, patients undergoing basal insulin therapy, therapeutic use of the Ultra long-acting analogue of basal insulin requires careful evaluation regarding economic burden and its impact, especially suggested for patients who are concerned about injection frequency. (22)

The Ultra long acting analogue of basal insulin indicated comparable effectiveness and tolerability to daily administered basal insulin in India, individuals with diabetes mellitus (type 1 and type 2). The available evidence suggest that icodec is a suitable choice for initiation of insulin therapy or intensifying insulin therapy in Indian healthcare settings. (10)

Weekly administration of the Ultra long acting analogue of basal insulin attained greater decline in glycated hemoglobin (HbA1c) with more patients achieving HbA1c glycaemic goals compared with daily administered basal insulin analogues. No significant tolerability consideration were recorded regarding hypoglycaemia episodes and undesirable effects. (2)

Insulin icodec, due to its characteristic molecular and pharmacological properties, offers and advanced once weekly treatment option for diabetes mellitus, and serving as a key innovation in therapy. (1)

Once weekly insulins represent the latest innovations in long-acting insulin therapy and has the ability to achieve a major change in treatment. (5)

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