

CLINICAL EVALUATION: LITERATURE ROUTE
For the Injex Needleless Injection System

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CLINICAL EVALUATION: LITERATURE ROUTE For the Injex Needleless Injection System

1.0 PURPOSE:

The purpose of this document is to summarize the available clinical data for the Jet Injection Systems and in particular the Injex Needlefree Injection System to determine if the devices are safe and effective for their intended use.

2.0 ABBREVIATIONS, ACRONYMS AND DEFINITIONS OF TERMS

FDA Food and Drug Administration
EU European Union
US United States

3.0 INTRODUCTION

Individuals with type 2 diabetes require insulin treatment when an appropriate combination of oral antidiabetic agents (OAD's) and lifestyle changes fail to provide adequate glycemic control. Eventually, many individuals with type 2 diabetes, not unlike individuals with type 1 diabetes, require multiple daily injections (MDI) therapy to achieve optimal diabetes control.

As an alternative to the uses of syringes, needle-free jet injectors were developed in the 1940s and were implemented for mass inoculations, most notably by the military (A). In recent years, state and federal legislation has encouraged the development of safer injection products and jet injection technology has gained momentum in multiple clinical areas as a result. For example, jet injectors have been used for heparin administration (B), insulin administration in Type I diabetics, (C,D,E), delivery of pain medications such as midazolam (F,G), and in vivo gene introduction for gene therapy (H).

The Injex Injection System has marketing clearance from the US Food and Drug Administration. The device utilizes a spring mechanism to propel 0.05 mL to 0.50 mL of solution through a 0.007 inch orifice under a pressure of 3,000 PSI. This 'liquid needle' has sufficient force to pass through the skin and enter the subcutaneous tissue to a depth equivalent to delivery via standard needle syringe. Further, the device utilizes a low cost, single-use disposable cartridge called an 'ampule' which minimizes the potential for cross-contamination, a serious issue which has been observed with jet injectors employing multi-use components. Loading of the ampule is performed with a vial adapter device but is otherwise identical to drawing medication into a syringe.

Indications for Use

The Injex System is designed to deliver various medicines and vaccines by means of a narrow, high velocity jet of fluid which penetrates the surface of the skin and delivers the medicine or vaccine to the body.

Contraindications

There are no contraindication for use of the Injex Needlefree Injection System

Warnings, Precautions

Potential risks to the user include inadequate delivery of the medication due to wet shots and/or residual medication in the ampule.

Repeated use of the Ampule will cause wet shots or Ampule failure and could result in injury to the user.

For insulin use

The Injex Injection System is designed for use with U-100 insulin only.

Injex Injection System users may experience faster absorption of insulin compared to needle injection. Discuss any change in the insulin dosage or delivery system with your physician or healthcare professional before use

The user should check their blood sugar levels more frequently when making any change in dose or delivery system to be sure that your control goals are being met.

Complications from inadequate delivery of the medication include: Extreme thirst, Lethargy, Frequent urination (due to high blood glucose levels), Nausea, Vomiting, Abdominal pain, Progressive drowsiness, Deep, rapid breathing and/or a fruity or acetone smell on the breath. If not treated, insufficient insulin may cause the subject to go into a coma.

Product Description

The Injex-Equidyne Systems Injex Injector System is a means of administering subcutaneous medications without the use of needles. The needle free injector utilizes a high velocity focused jet of liquid to penetrate the skin and deposit the medication in the subcutaneous tissue. The process takes place in a fraction of a second. Needle free injection is useful in a wide range of drug therapy including immunization vaccines, hormones and local anesthetics, as well as the administration of insulin to the diabetic population, where individuals may need a number of injections per day.

The Injex Needlefree Injection system consists of four main components;

1. Injex Injector - A small re-usable hand held Injector,
2. Injex Reset Box - A compact re-usable Reset Box used to reset the Injex Injector,
3. Injex Ampule - A disposable, sterile Ampule that functions like a needle syringe to draw the medication from the medicine bottle or vial using a hand draw with a plunger. Once the Ampule is loaded into the Injex Injector, the dose is injected into the individual by releasing the Safety and pressing the trigger.
4. Injex Adapter - A disposable, sterile Vial Adapter facilitates the transfer of the medication from the medicine bottle or vial to the Ampule.

The Injex Injector can deliver variable doses of fluid medication from 0.05 ml to 0.50 ml. The injector has two safety mechanisms. The first safety mechanism is automatic and prevents the injector from discharging the medicine in the Ampule unless the Ampule is fully screwed into the injector. The second safety mechanism is a Safety Ring that is manually slide under the Trigger of the injector and prevents discharging the injector unless the Safety Ring is manually slide forward.

4.0 CLINICAL PHARMACOLOGY

4.1 Performance Testing of the Injex System

Performance tests conducted with the Injex System examined the effects of needle-free jet injection on the structure of administered compounds, the depth of tissue penetration and the histology of tissue surrounding the injection site. Following is a summary of those studies:

Retention of Structural/Potency Characteristics of injectable drugs and model compounds (1)

The objective of these studies was to determine whether model compounds retain their physical characteristics post-injection with the Injex Needle-free Injection System. Comparisons to delivery via a control as well as a standard syringe will be performed.

The compounds investigated encompassed a range of molecules from small (< 1,000 Daltons) to large (close to 1 million Daltons). Model compounds comprise the majority of materials tested;

Drug – Thyroxine (molecular weight 776.9 Daltons). This compound is equivalent in molecular weight, structure, and purity to Synthroid, which is commonly marketed by Boots Pharmaceutical, Inc.

Model compounds – To investigate molecular damage across a wide range of compound molecular weights. The compounds tested included the following:

1. Cyanocobalamin (Vitamin B-12) – 1,350 Daltons
2. Myoglobin – 17,000 Daltons
3. Ovalbumin – 44,000
4. Immunoglobulin G (bovine) – 158,000 Daltons as a monomer
5. Thyroglobulin – 670,000 Daltons as a dimer

In all analyses, samples delivered by the Injex System are equivalent to Control solutions. These Control solutions were pristine stock solutions that had encountered neither the Injex System, nor a syringe. Based on the High Performance Liquid Chromatography and Polyacrylamide gel electrophoresis data, the use of the Injex System does not cause loss of molecular structure, molecular weight, or molecular change characteristics. The Thyroxine immunoassay shows that use of the Injex System does not cause any change in immunoreactivity which, after all, is a function of molecular structure, conformation, and other physical characteristics.

Retention of Structural/Potency Characteristics of Insulins (2)

Insulins investigated encompassed a range of sources (porcine, bovine, human recombinant), activities (rapid acting, short acting, intermediate acting and long acting), formulations (solutions, crystal suspensions) and manufacturers (Eli Lilly, Novo Nordisk). The normal concentration (label claim) for all drugs is 100 units/milliliter (U/ml).

The compounds tested included Humalog, Velosulin, Humulin R, Novolin R, Lente Iletin I, Humulin N, Humulin L, NPH Iletin I and Humulin U, Lantus Insulin.

The in-vitro study demonstrated complete retention of molecular identity of insulin molecules injected via the Injex System. Multiple types of insulins were explored including insulins from varying sources, of varying activities, of varying formulations, and produced by various manufacturers. In each case, the immunoreactivity was retained, thus suggesting that epitope moieties were maintained intact despite the high pressures of injection utilized by the Injex System methodology. It is logical extension that if epitopes are maintained intact, that the overall primary and secondary structure of the molecule is likely intact. To explain further, molecular epitopes for peptide/protein molecules are generally on the order of tens of amino acids. Since insulin is a dipeptide on the order of 50 amino acids, it is unlikely that any shearing can have occurred.

Further, protein epitopes are generally required to be in a three dimensional conformation consistent with the original antigen used to produce and select antibodies. Since there is no loss of immunoreactivity in this study, the three dimensional conformation (tertiary structure) of the molecule is also maintained after injection. This is a profound finding since insulin is a complex dipeptide protein with two disulfide bridges linking the polypeptide chains. It is therefore logical to conclude that structural damage (cleavage of the disulfide bonds or unwinding of the tertiary structure) has not occurred as a result of injection.

Animal Studies (3,4)

The aim of this study was to investigate the suitability of the Injex System for the subcutaneous injection of medicines. To this end the depth of penetration of a dye solution (ink) was determined following injection of different volumes into the forelimbs of pigs killed prior to being butchered and the distribution of the dye was investigated histologically.

Different volumes of a dye solution were applied with injectors with different spring forces. The results showed that the depth of penetration was dependent on the applied volume. The experiment showed that volumes up to 0.3 mL can be applied reliably and strictly subcutaneous. In all instances except one the epidermis at the injection sites remained intact, no damage of the underlying tissue or edema were observed. The injected doses were located in the subcutaneous compartment as a cone-like structure. The penetration depth reached from 3.2 mm (application volume: 0.05 mL) to 7.4 mm (application volume 0.20 mL).

In an additional series of tests the absorption kinetics of heparin following injection with the Injex System were recorded and compared with those after subcutaneous injection using a conventional needle.

In this study the absorption experiments result in comparable adsorptions after injection of HMW-heparin with the Injex System or with a conventional needle. After administration with the Injex System the heparin concentrations in the perfusate are somewhat lower than after injection with the needle system. The maximum heparin concentration is attained 3-4 hours, corresponding to already published data. (6)

5.0 CLINICAL STUDIES

The Injex System is intended to be used with various medicines and vaccines with molecules in the 1,000 to 1 million Dalton range. A search of the literature shows that since the 1940s various medicines and vaccines have been injected by means of jet injection. This clinical evaluation summarizes the data from these studies to determine the safety and effectiveness jet injector for the delivery of various medicines and vaccines. As part of the evaluation, patient risks and satisfaction will be assessed.

Vaccines (5,6,7)

Use of the Injex System for delivery of the Measles, Mumps, and Rubella Vaccine (MMR vaccine)

The MMR vaccine (Merck and Co.) for immunity to Measles, Mumps and Rubella virus is one of the most widely used vaccines in medical practice. The standard delivery method is subcutaneous injection of 0.5 mL of vaccine delivered with the Injex System.

The study objectives were:

1. Comparison of antibody titers to Measles, Mumps and rubella in subjects receiving the vaccine via the Injex System vs. subjects receiving the vaccine via a standard needle syringe.
2. Comparison of pain responses in subjects receiving injections via the Injex System vs. needle syringe.

In this study, 40 adolescent subjects were injected with the vaccine and followed for 3 months. A baseline blood draw was performed to determine pre-vaccination immunity to the virus. After injection with either the needle syringe or Injex System, subjects returned 1, 2 and 12 weeks after injection for a blood draw.

For pain measurements, it was necessary to also administer the buffer used to reconstitute the MMR vaccine. Each subject received two injections at the Day 0 timepoint; an injection of MMR vaccine either with the Injex System or the needle syringe, and an injection of reconstitution buffer either with the Injex System or the needle syringe. The study was single-blinded in that subjects were unaware which injector contained the vaccine. Pain scores were determined using the Visual Analog Pain Scale.

The results of the study showed all subjects with measles titers significantly above baseline during the follow up. Ninety-five percent of the subjects displayed titers above baseline for the mumps antigen vs. 97.5% for rubella. In addition, there were no significant differences in immunogenicity between groups receiving the vaccine via the jet injector or the needle syringe at any time during the study.

There was a general trend toward increased percentage of subjects responding with the Injex System, but it wasn't significant. In addition, there were no significant differences between individual or combined groups with respect to antibody titer.

Analyses of pain scores from the visual analog pain scale showed no significant differences between groups ($P > 0.05$). The results may have been more of an effect of the pain due to the vaccine/buffer formulation than to differences between injector type.

Adverse events were mild and included injection site soreness (jet injector 2.5% vs. needle 12.5%), injection site bleeding (jet injector 0% vs. needle 7.5%), malaise (jet injector 0% vs. needle 5%), and fever (jet injector 0% vs. needle 2.5%).

Medicines – Insulin (8,9,10,11,12,13)

There have been numerous studies comparing insulin levels after subcutaneous administration of insulin by Jet Injector and conventional needle injection. In one study conducted by the Mayo Graduate School of Medicine in Rochester, MN, the plasma insulin profiles of eight subjects (7 female and 1 male) whose ages ranged from 20 to 48 years (mean age = 32 years old) was compared after insulin injections using Jet Injection and conventional needle injections. After each insulin injection, blood specimens were taken every 10 minutes for the first hour, every 15 minutes during the second hour and every 30 minutes for the next 3 hours.

The results showed that the baseline insulin concentrations were not significantly different before jet injection (12 ± 2 uU/mL) and needle injection (13 ± 2 uU/mL) of insulin. Between 10 and 60 minutes after administration of insulin, however, plasma free insulin values were greater ($P < 0.05$) after jet injection than after needle administration. The study also showed that plasma free insulin concentrations between 75 and 150 minutes after injection were not significantly different with the two methods of administration of insulin, subsequent concentrations were less after jet injector administration of insulin than after needle administration ($P < 0.05$).

This study demonstrated that administration of insulin with the jet injector to patients with insulin dependent diabetes mellitus produces more rapid and less prolonged increases in plasma free insulin concentrations than does conventional subcutaneous injection of insulin. Thus, administration of insulin with a jet injector may be considered as a useful alternative to subcutaneous needle injection of insulin or pump administration of insulin inpatients who prefer to use these modes of insulin delivery or in whom these methods do not produce satisfactory glycemic control.

The company sponsored a study to evaluate the pharmacokinetics and glucodynamics of rapid, short and intermediate acting insulins delivered via needle syringe and the Injex Needle-free Jet Injector. This study employed the euglycemic clamp technique in a cohort of healthy volunteers as a model for insulin effects in patients with diabetes. Each member of the cohort of 16 subjects received a rapid acting insulin (Humalog) in phase 1, short acting regular insulin (Humulin-R) in phase 2, intermediate acting NPH (Humulin-N) during phase 3 and pre-mixed insulin (Humulin 70/30) in phase 4. Mean subject age was 40 years and the mean body mass index was 23 kg/m^2 .

The results of this study demonstrate minimal differences in pharmacokinetic and glucodynamic properties of exogenous insulins delivered via jet injection in comparison with needle syringe. The study did show a slightly more rapid glucose lowering effect following jet injection of rapid and short acting insulins. All other parameters are essentially equivalent. Thus, the study found that the Injex Needle-free Injection System may provide a safe and effective alternative to needle delivery.

Another study evaluated the feasibility of using a jet injector in a split and mixed regular and NPH insulin regimen and to compare serum glucose and free insulin profiles obtained with the Jet Injector and conventional needle syringe. Twelve insulin dependent diabetic patients participated. The mean age was 24.5 years and the mean duration with diabetes was 10.2 years.

A three factor analysis of variance was performed on the serum glucose profile. Results showed that both groups were similar ($P = .290$). An analysis of variance showed no significant difference ($P=.477$) on the order effect. The results showed that injector serum glucose profiles were significantly lower ($P=0.010$) than those obtained with a conventional syringe. In contrast, serum free insulin levels were significantly higher ($P=.05$) with the injector than the syringe.

The objective of this study was to compare the serum glucose and free insulin profiles obtained with the injector and syringe by use of a split and mixed regular and NPH insulin regimen with both methods. The results demonstrated that the use of a jet injector for such a regimen is feasible. Consistently lower serum glucose throughout the day followed by an increase at the end of the day suggested that insulin absorption was faster with the Jet Injector.

In summary, the characteristics of plasma free insulin profiles after conventional subcutaneous injection of insulin and after jet injection after injections of similar doses have been compared in many studies with subjects having insulin-dependent diabetes mellitus. A common finds among studies showed that although administration of insulin with the jet injector resulted in peak plasma free insulin concentrations similar to those achieved after conventional injection, it produced more rapid increases in plasma free insulin concentrations (time to peak concentrations) and less prolonged hyperinsulinmia. Variability in the peak insulin concentrations and the time to peak concentration was comparable for both methods of administration of insulin. Thus, insulin administered by jet injector may improve control of postprandial hyperglycemia and diminish the risk for late hypoglycemia in some patients with insulin requiring diabetes mellitus treated with conventional injections of insulin.

Additional Applications

Pharmacokinetics of Low-Molecular Weight Heparin following Needle-free and Conventional Subcutaneous Injections (14)

A study at Medical University Clinic Gottingen examined the absorption of low-molecular weight (LMW) Heparin after subcutaneous injection by Jet Injector and needle syringe. The study population consisted of 12 healthy volunteers who were administered LMW using the traditional needle syringe the first week and the Jet Injector the second week.

The results showed that 11 of the 12 participants displayed an almost simultaneous rise and fall of the factor Xa activity when comparing both of the application methods. On average, the single values were higher at all given times of measurement when the Jet Injector was used.

The conclusion of the study was that a Jet Injector could be used to achieve LMW Heparin absorption very similar to that of the pen. Haematomas were observed both with the Injex Needle-free Jet Injector and the needle syringe. The study concluded that the Injex Needle-free System is well suited for realizing a safe and reliable prophylaxis against thrombosis.

A preliminary study using the Injex System with local anesthesia.(15, 16)

This study examined the feasibility of administering xylocaine or bupivacaine or its isomers with the Injex Needle-free Jet Injector subcutaneously for field, ring or sensory nerve block anesthesia.

A majority of patients felt no pain sensation during the injection. Patients reporting a stinging discomfort had injections mostly over bony prominences. The onset of anesthesia in almost every instance was noted to be as fast or faster than conventional injections using a needle syringe.

The conclusion of the study was that the Injex Jet Injector offers advantages over the subcutaneous infiltration of -caine anesthetics via syringe and 30 gauge needle whether used with or without Fluori/methane.

Clinical Pharmacology Conclusion

The data shows that the pharmacokinetics of various vaccines and medicines are similar after administration via the Injex Needle-free Jet Injector or a conventional syringe. Furthermore, bioequivalence was confirmed between the two administration methods. Therefore, it can be concluded that various vaccines and medications administered using the Injex Needle-free Jet Injector is bioequivalent to various vaccines and medications administered by conventional subcutaneous injection.

6.0 ANALYSIS OF EFFICACY

No efficacy data was recorded in the clinical studies. However, the efficacy of each vaccine and medication tested is well established. Since bioequivalence was confirmed with regards to the Injex System to the conventional subcutaneous injection, it can be assumed that the clinical efficacy of the vaccines and medications administered by the two injection systems would also be equivalent.

7.0 ANALYSIS OF SAFETY

Injection Site Symptoms

A review of data for a growth hormone study focused on the incidence of injection site bleeding which was the primary response variable. The results for symptoms of pain, bruising and soreness were similar to those for bleeding and non-inferiority was not met.

Study results showed 45.3% of patients considered the average bleeding severity with the Injex to be mild at the time of injection compared to 10.3% patients with the needle device. In addition, 2.6% of patients considered the average bleeding severity with Injex to be moderate compared with no patients with the needle device. All other patients considered the average bleeding severity at the time of injection as None.

Overall, the results of injection site bleeding did not support the hypothesis of non-inferiority of Injex to the needle device. Moreover, a two-sided comparison showed that Injex was statistically inferior to the needle device when bleeding was analyzed as part of the study. The study noted that over 50% of participants thought that injection by either needle or Injex were the same, demonstrating acceptable tolerability of the needle-free device.

Adverse Events

In the Genotropin Study, adverse events were reported in at least 1% of patients in either treatment groups. The frequency of adverse events was low with both the Injex (22%) and the needle devices (13.1%). Exclusion of device failure not otherwise specified (wet shots, clear liquid spilling out of injection hole) from the adverse event data showed that the overall frequency of adverse events was similar for the Injex patients (15.2%) and needle devices (12.3%).

The majority of adverse events were of mild or moderate intensity. No deaths or serious adverse events were reported. Two patients discontinued study medication due to adverse event. None were device related.

Adverse Events of Device Failure

Any adverse events associated with the use of the Jet Injector was of interest in the study. The most frequently reported adverse event was the device failure (wet shots, clear liquid spilling out of injection hole), which involved the appearance of clear fluid at the injection site administration of study medication. Only two of the 16 device failure events were considered related to the drug/device.

Although the majority of device failure events occurred with Injex, this may be associated with the injection technique and/or relative inexperience of the patient in using Injex compared with their current needle-injection device, rather than failure of the device itself.

Safety Conclusions

Overall, the needle injection devices performed better in a majority of the studies with a population of patients already comfortable with needle injection. The majority of patients found the Injex to be the same as needle in terms of the major parameters of bleeding, pain, soreness and bruising. Both the injex and the needle devices were well tolerated, with a low incidence of adverse events reported for each device. There were no deaths or serious adverse events. The incidence of device failure adverse events were higher with the Injex, although this may have been due to the patient's relative inexperience of using the Injex device compared with their usual needle device.

8.0 POSTMARKETING EXPERIENCE

Injex-Equidyne Systems, Inc. reviewed all Customer Complaints and Feedback. Since the introduction of the Injex System in 1999, there have been no deaths and/or serious injuries, product recalls or Field Corrective Actions.

A review of all available information showed no malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health.

In addition, there are no technical or medical reasons connected with the characteristics or performance of the Injex System that would lead to a systematic recall of the device by the manufacturer.

9.0 BENEFIT-RISK ASSESSMENT

The rationale behind the development of the Injex Needle-free System is to offer patients and healthcare providers the option of a needle-free method of injection for patients who currently receive a vaccine and/or medication by pen injection or conventional syringe.

The data presented in this report show the pharmacokinetics for the various vaccines and medications are similar after administration via the Injex needle-free device or a conventional syringe. Furthermore, bioequivalence for the various vaccines and medications was confirmed between the two administration methods. Therefore, it can be concluded that various vaccines and medications administered using the injex System is bioequivalent to vaccines and medications administered by conventional subcutaneous injection. It is therefore likely that the clinical efficacy of vaccines and medication would also be equivalent whether administered via Injex or a needle device.

In the presented studies, non-inferiority of Injex compared to a needle device for the administration of vaccines and medications could not be established statistically for assessment of injection site symptoms (bleeding, pain, soreness and bruising). In addition, there was evidence to show that Injex was statistically inferior to the patient's current needle device. These findings need to be placed in context with regards to the device experience and characteristics of the patient population. Patients were not needle phobic and were skilled in using their current needle device.

Both the Injex and needle devices were well tolerated, with a low incidence of adverse events reported for each device. Although the incidence of device failure adverse events was higher with Injex, this may have been due to the patient's relative inexperience of using the Injex device compared with their usual needle device. In clinical practice, it is recommended that a patient would not switch to Injex until they were familiar with the injection technique and comfortable with using the device.

One of the potential benefits of the Injex device is that it obviates the risk of needle-stick injuries and may help eliminate the possibility of cross-contamination. In addition, it has been claimed that needle-free administration tends to lead to fewer adverse psychological responses than a multidose injection pen, which may be of benefit to those patients unable, unwilling or who have no desire to use needles.

10.0 CONCLUSIONS AND RECOMMENDATIONS

The results of this analysis suggest that administration of various medications and vaccines with the Injex System is equally as efficacious as administration with a standard needle syringe. This is reflected by the statistically equivalent titers to measles, mumps, and rubella antigens expressed at multiple time points in the cohort as well as the pharmacokinetic studies with insulins.

The analysis of pain response appears to be problematic and confounded due to pain caused by the medication/vaccine/buffer formulation itself. It is therefore unlikely that firm conclusions can be drawn from the studies.

In summary, this clinical evaluation has presented evidence that the pharmacokinetics of various medications and vaccines when injected by jet injection is equivalent to an injection by a needle syringe. Therefore, injection of various medications and vaccines by Jet Injection is safe and effective.

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