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Perspectives on Commercialisation of Oral Insulin

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ABSTRACT

The objective of this paper is to demonstrate that oral insulin is potentially close to being commercialized, in light of the fact that (i) the technical, safety, and pharmacological obstacles in developing an oral insulin for clinical use for diabetes can potentially be overcome, and (ii) there are players in the field that are moving an oral insulin formulation into advanced clinical trials.

Introduction

Oral insulin has been a key goal for pharmaceutical scientists since the first demonstration by Banting and Best in 1921 of the ability of insulin to treat diabetes[1]. The many advantages of oral insulin over injected insulin, as well as other therapeutic options, has been the subject of a recent review[2], which also identified the benefits of targeted absorption pathways via the portal vein direct to the liver. However, overcoming the many hurdles to oral delivery of insulin (and other larger proteins) has proved so challenging that it is only recently that approaches have been developed which are demonstrating promising efficacy with pharmaceutical formulations which are therapeutically and commercially viable.

Previous reviews of the field[3-5] have provided updates on progress, particularly in relation to preclinical studies of potential delivery platforms up to 2020. However, in the last five years, clinical studies have demonstrated significant progress, with several phase 2b studies having been completed, and the prospect of phase 3 studies commencing soon in various parts of the world. Contrary to previous preconceptions, the advances required to make oral insulin a reality are not improvements in bioavailability/ efficacy, but the development of delivery formulations which avoid components with toxic side effects, are simple to manufacture, and demonstrate good stability. An exhaustive literature search was conducted to identify all published data relating to clinical trials with oral insulin in diabetes patients. This information is used as the basis for discussion of the points outlined above.

Discussion

One aspect to be aware of is that oral insulin, under the guidance of regulatory authorities such as the FDA, is to be considered initially for treatment of Type 2 (non-insulin dependent) diabetes, rather than Type 1, and that it will be not just a replacement of injected insulin, but will be used in parallel to other oral anti-diabetes treatments at the early stages in progression of the disease. Type 2 diabetes constitutes approximately 85% of the total diabetes market, and early-stage treatments are at least 70% of the total market.

While the analysis below focusses on Type 2 diabetes, there is every reason to believe that oral insulin may have a role to play in Type 1 diabetes as well. On an empty stomach, an enteric-coated capsule can pass through the stomach within ten minutes, and open up in the small intestine a few minutes thereafter. Consequently, a capsule taken shortly before a meal will provide insulin to the liver at the same time as a glucose spike is produced as a result of food intake. It is important to recognise that HbA1c, reflecting long-term glucose control, is a function of blood glucose levels in the prolonged periods in between meals, rather than the spikes just at mealtimes. Since the action of oral insulin in the liver can last for at least nine hours[2], the treatment will be effective in controlling the overall glucose elevation regardless of rapidity of onset. Consequently, once further progress has been made with treatment of Type 2 diabetes, attention will no doubt be turned to the challenge of treating patients with Type 1 diabetes.

Five factors determine the likelihood of any oral insulin coming to a broad market: (i) safety and in particular with respect to avoidance of hypoglycemia (ii) biopotency (or bioavailability in the portal vein) of the formulation, (iii) price to the patient, (iv) cost of oral insulin manufacture and (v) availability of the insulin raw material.

*(i) **Safety.*** Insulin administered orally on its own gives rise to no safety concerns, as shown in a number of long-term studies[6-7]. In all the oral insulin programmes which have progressed the furthest, safety, has not been an issue. Neither in those studies using new chemical entities as absorption enhancers (Novo, Biocon) nor those where enhancers are natural products or food additives (Diabetology, Oramed) were any significant untoward treatment-associated-side effects seen. For example, with the Diabetology formulation, no incidence of

hypoglycaemia was reported in 25,000 dosing events in intent to treat patient population of 150, despite the fact that one would expect to see significant incidence in that number of patients receiving insulin by injection[8].

The absence of 'beyond physiological' quantities of insulin entering the outer circulation with oral insulin is an indication for a successful formulation, not a failure. Oral insulin exerts its effect by stimulating receptors in the liver, and whilst it does need commercially viable quantities entering the targeted blood vessels (eg portal vein), it has no need for high levels in the outer circulation, in contrast to injected or 'non-portally' delivered insulins; insulin which leaves the portal vein is absorbed by the liver rather than entering the outer circulation. In contrast, injected insulin leads to prolonged hyperinsulinaemia which brings about a range of toxic side effects, including cancer, inflammation weight gain, retinopathy etc[9-10]. In the successful later-stage studies listed in this paper, the fact that HbA1c falls have been achieved indicates that hyperglycaemia is not occurring, and this is confirmed by falls reported in fasting plasma glucose. Reproducibility of biological activity of oral insulin has been studied in clamp studies[2,11] and shown to be as good, if not better, than when insulin is administered via injection. Taken together, these observations indicate that there is no reason to expect hyperglycaemia or hypoglycaemia (in the case of portally-delivered insulin) to be toxic side effects of oral insulin treatment.

(ii) ***Biopotency***. In cases where the major site of action of a drug is not the bloodstream, relative biopotency, rather than outer circulation bioavailability, is the important criterion to use when comparing the activity of different formulations. This is due to the ethical and practical difficulties of performing portal assays in humans. This is particularly relevant with insulin, where a major site of action is the liver, and where only a small amount reaches this organ when administered via parenteral injections, whereas all of the insulin produced by the pancreas passes via the portal vein directly to the liver. In this case, biopotency of oral insulin is defined as the biological result observed (ie HbA1c reduction/glucose lowering) when insulin is administered via the oral route relative to when insulin is administered by injection. In a normal healthy individual, the daily output of insulin from the pancreas to the liver is about 45iu, and this corresponds closely to insulin usage of type 2 diabetes patients taking insulin by injection, who typically take between 40 - 60iu on a daily basis. Recent trials with oral insulin have achieved clinically significant outcomes with doses of 300iu (10mg) daily[8], suggesting a biopotency of between 10 and 20%. This is corroborated by results of preclinical studies looking at the bioavailability in the portal vein of proteins administered via the intestine, which can reach 19% (New et al 2024). One feature of oral insulin which is often overlooked is that, because of its mechanism in stimulating glucokinase synthesis in the liver, the liver is able to match its activity to the concentration of glucose in the bloodstream, and there is no need to titrate insulin on the basis of glucose tests or carb intake[2].

(iii) ***Price paid by the patient***. The pricing of insulin-based treatments is currently in a state of flux. In recognition of the fact that, for Type 1 diabetes, where insulin is the only available treatment, a price cap in US on out-of-pocket (OOP) costs to the patients, possibly as low as $35 per month, is in place. In government assisted health programmes such as Medicare and Medicaid in US, the taxpayer contributes ~60% of the cost of the medication, meaning that, taking the price cap into account, the retail cost of the treatment could be ~$100 per month. For insulin analogues this can be much higher, for example 75iu insulin degludec (Tresiba) taken daily would cost around $25

per day. In territories, including Europe, where QALY (Quality-Adjusted Life Years) calculations, or similar, are used to assess pricing, an early-stage oral diabetes treatment such as oral insulin, with QALY advantages, could be priced at an equivalent level to SGLT2 inhibitors, where a cost of $15 per day to the patient would be justified. Which of these scenarios any oral insulin could fit into (including reimbursement, after negotiation with all parties involved) may be determined by the pricing from manufacturers of the insulin itself, together with the demonstrable cost/benefit calculations such as QALY benefit comparatively over injected insulin or OAD's where avoidance of hypoglycemia, reversal of FPG below baseline and reduction of triglycerides may have wider economic and patient benefits.

(iv) ***Cost of insulin to manufacture***. It is worth noting that some oral insulins (eg Diabetology's Capsulin) exhibit properties which are akin to long-acting injected insulins, so oral insulin, which uses the cheaper recombinant human insulin (RHI) can benefit from economies using RHI rather than the much more expensive APIs glargine, degludec or detemir (see Gotham et al[13] for price comparisons). The same source shows that production costs for the insulin vial and associated injection devices can be four times that of the RHI itself. In contrast oral insulin capsules/tablets can be much cheaper to produce because of the absence of need for sterile processing etc. Consequently, although oral insulin formulations contain more API than injected, the overall cast of the final product may not be very different on a daily basis. The price of RHI raw material has been coming down progressively over time, and with new production techniques and, allowing for discounts applied to locally manufactured material rather than imported, it is conceivable that pricing could come down from $70k/kg in 2016 to $20k/kg beyond 2026, which would support an oral product to be affordable at a cost per month to the patient for a $35 price cap restriction and in any event for use outside of these restrictions in each country. It is generally considered that a biopotency of around 10% would meet this requirement. For additional insight on pricing and affordability in different territories, see Barber et al[14], Beran et al[15] and Van Nuys et al[16].

(v) ***Insulin availability***. While there is currently an undersupply of proprietary long and short acting insulins with significant investments being made in this area such as Sanofi in China. Costs of manufacture in western countries have still yet to fully reflect efficiencies and trends for use of standard RH Insulin as a biosimilar are that both these factors will rectify themselves in the future as measures are being taken to overcome any resultant shortages caused by significant need for a successful oral insulin. 90% of insulin is currently manufactured by the three large pharma Novo, Lilly and Sanofi, but other producers are coming on-line to boost production, and provide extra capacity. Civica has recently commenced manufacture in the US, and supplies of insulin are also available from companies such as Biocon/Viatris and MJ Biopharm/Eris, with DMFs for the US market. A number of companies in China (eg Tonghua Dongbao, Ganli, Yifan,TUL), Europe (Bioton) and the Middle East (Julphar) also have capacity which may, if necessary, be scaled up cost-effectively. In addition, for a large pharma wanting to enter the (oral) insulin market, it would not be uneconomic for them to set up or expand their own manufacturing facilities, given that the production process for recombinant human insulin has been refined over 20 - 30 years, and is relatively low cost compared with other proprietary insulins and biologics.

It is clear, therefore, that there is in principle no impediment to taking an oral insulin to the market, and the final piece of the puzzle is which technologies

have successfully reached the final milestone, and have conducted human trials demonstrating clinical success with formulations which are commercially viable. The progress made toward this goal is encapsulated in the accompanying table, showing an overview of all major reported studies to date. In this table it can be seen that a number of studies have been carried recently which have achieved significant falls in HbA1c and glucose, as well as FPG, and in one case, falls triglycerides[8].

Clinical Trials with Peer-Reviewed Published Data on Oral Insulin Efficacy in Patients with Diabetes (in Chronological Order)

Company	Insulin API‡	Phase	N	Duration*	Site	Type	Dose (mg)	Endpoints Achieved	Status	Reference
Nobex	Pegylated	2a	16	2 x SD	US	1	≥50**	Glucose, insulin	Discontinued	[17] Clement et al (2002)
Nobex	Pegylated	2a	18	SD	US	2	≥25**	Glucose, insulin	Discontinued	[18] Kipnes et al (2003)
Nobex	Pegylated	1/2a	16	SD	US	1	≥40**	Glucose, insulin	Discontinued	[19] Clement et al (2004)
Emisphere	Rec. human	2a		14 days	Germany	2	10 QID	Insulin	Discontinued	[20] Heise et al (2004)
Diabetology	Rec. human	2a	8	SD	UK	1	5 or 10	Glucose, insulin	Active	[21] Whitelaw et al (2005)
Emisphere	Rec. human	2	144	90 days	ND	2	5 or 10 BID	HbA1c	Discontinued	[22] Goldberg (2007)
Diasome	Rec. human complex	2		14 days	US	1	ND	ND	Discontinued	[23] Schwartz et al (2008)
Diasome	Rec. human complex	2a	6	SD	US	2	0.13 to 1 escalating	glucose	Discontinued	[24] Schwartz et al (2008)
Diabetology	Rec. human	2a	16	SD/10 days	UK	2	5 or 10 BID	GIR, weight, HbA1c	Active	[11] Luzio et al. (2009)
Emisphere	Rec human	2a	10	SD	Germany	2	10	GIR	Discontinued	[25] Kapitza (2010)
Biocon	Pegylated	2a	40	SD	India	2	10, 15, 20 or 30	Glucose, insulin	On hold	[26] Khedkar et al (2010)
Oramed	Rec. human	2a	8	10 days	Israel	1	8	Glucose (CGM)	Active	[27] Eldor et al (2013)
Oshadi	Insulin/proinsulin/C-peptide	1	8	SD	Israel	1	5 or 10 BID	Glucose lowering	Discontinued	[28] Rachmiel et al (2019)
Oshadi		1b	10	2x3 days	Israel	1	5 or 10 BID	Glucose lowering	Discontinued	
Oshadi		2a	16	4 weeks	Israel	1	5 or 10 BID	Glucose lowering	Discontinued	
Novo	Long-acting basal	2b	50	8 weeks	Germany	2	Up to 33 escalating	FPG	Discontinued	[29] Halberg et al (2019)
Biocon	Pegylated	1	51	SD	US	2	30	Glucose, insulin	On hold	[30] Khedkar et al (2020)
Oramed	Rec. human	2a	188	28 days	?	2	16 or 24 BID	HbA1c	Active	[31] Eldor et al (2021)
Biocon	Pegylated	2/3	91	24 weeks	India	2	30 or 45 TID	PPG	On hold	[32] Lebowitz et al (2022)
Oramed	Rec. human	2b	373	12 weeks	US	2	8, 16 or 32 QD/BID	HbA1c	Active	[33] Eldor et al (2022)
Diabetology	Rec. human	2b	100	12 weeks	India	2	5 or 10 BID	HbA1c, FPG, triglycerides	Active	[8] New et al (2022)

*SD = Single dose
**Doses reported in mg/kg. Figures given assume a body weight of 80kg
‡API is unmodified insulin unless otherwise stated
PPG – Post-Prandial Glucose
FPG – Fasting Plasma glucose
ND – Not disclosed

Novo completed a phase 2 study[29] in 2015, but concluded that, using sodium caprate as permeation enhancer, and a basal long-acting insulin, the quantity of active required to achieve the desired clinical outcome did not make for a product which would be cost effective for their company. In this escalating dose study, the final oral dose was ~1000iu per day, giving the same level of glucose control as 30iu of injected insulin glargine, and suggesting a low biopotency of about 3%. This, together with the higher cost of the long-acting insulin employed in the formulation, probably contributed to Novo's decision to discontinue the project. The dose of 1000iu per day equates to 33mg, which compares unfavourably with doses employed by Diabetology[8] (10mg) and Oramed[33] (16mg). It is notable that in this study incidence of hypoglycaemic events for the oral formulation was similar to that for injected insulin, which may suggest that insulin was passing into the outer circulation – perhaps via the stomach – rather than being delivered to the liver via the portal vein.

Biocon have employed a modified insulin (NCE) to encourage transcellular uptake, probably across the stomach wall, resulting in sharp peaks of insulin in the bloodstream appropriate for use pre-prandially[32]. The doses of insulin tested have been quite high (up to 45mg TID), but this may not hinder Biocon, since their insulin is synthesized in-house.

Oramed use a highly unsaturated oil formulation which acts as a permeation enhancer taking insulin across the intestinal cell wall via the paracellular route (opening the tight junctions). A BID dose of 8mg twice per day appears to be the dosage of their choice[33].

Diabetology uses excipients which inhibit breakdown of insulin by protease in the gut, and which also stimulate transcellular uptake and passage across intestinal cells within vacuoles, directing the insulin into the portal vein, and exhibiting properties of both prandial and long-acting insulins. 5mg of insulin (150iu) BID is the dose of choice[8]. It is an enteric-coated solid-dose formulation with stability at room temperature of at least six months, making it suitable for use in LMICs (Lower Middle-Income Countries). Two of the components (chenodeoxycholate and propyl gallate) mutually enhance their solubility at the low pH of the small intestine, and these two agents showed themselves to be markedly superior to capric acid (a common permeation enhancer) in preclinical studies using a GLP-1 receptor agonist J229 as the active for comparison[34]. Additional excipients enhance the efficacy of the combination many-fold, with a bioavailability in the portal vein[12] of 18%.

Both Oramed and Diabetology are looking to commence phase 3 studies in the near future, prior to market launch in various territories and are in discussions with the FDA and other regulatory authorities. It is important to note that, in contrast to some indications, the structure of a phase 3 study in diabetes is identical to that for phase 2, with the same endpoints, dose, patient populations etc, so that if one has completed a phase 2 study successfully, conclusion of phase 3 should be within reach, given an appropriate study design.

Other approaches have been trialed which are not expected to proceed to phase 3 studies (see Oshadi and Diasome in the table) and a number of preclinical studies have been reported, mainly using nanoparticle approaches[35], but whether they will complete phase 3 studies in a timely fashion, and demonstrate any efficacy, safety or QALY advantages over the programmes described above is an open question. It is worth mentioning that nanoparticles, if they pass through into the portal vein, will be taken up preferentially by the Kupffer cells in the liver, rather than interacting with hepatocytes, so this approach may be flawed. It is certainly clear that nanoparticles are not the only option for delivery of insulin, and noteworthy that none of the most advanced platforms described above are based on nano-particle systems. See Bhattacharjee[36] for a summary of other problems with the nanoparticle approach.

Conclusion

While the use of injected insulin is limited by its potential side effects (even in patients using insulin pumps) including hypoglycaemia, macro and microvascular issues etc, the situation with some oral insulins is completely the opposite. Removal of risk of hypoglycaemia, together with avoidance of hyperinsulinaemia, mean that oral insulin can be a safer option suitable for use at all stages in the progression of diabetes, and, mimicking the route of entry into the liver of natural endogenous insulin, differs from all other treatments in terms of absence of side effects. For other medications these can include weight gain (sulphonylureas), GI effects (GLP-1 RAs) fracture risk (TZDs, SGLT2 and DPP4 inhibitors) reno/genito-urinary complications (metformin) or cardiovascular issues (sulphonylureas, TZDs).

The fact that oral insulin is able to satisfy the requirements of the liver without needing to rely on extra insulin secretion by the pancreas (in contrast to sulphonyl ureas, meglitinides, (and to some extent GLP-1 RAs) means that there is no risk of islet beta-cell exhaustion. As noted above, oral insulin can be priced competitively with other OADs, giving it an advantage over costly treatments such as GLP-1 RAs. Even in patients receiving GLP-1 RAs, there are arguments in favour of co-medication with oral insulin[12] because of the complementary activities of insulin and GLP-1 in the body. In particular, insulin markedly inhibits glycogenolysis, and enhances glucose uptake in the liver, while GLP-1 inhibits gluconeogenesis[37] and activates the portal vein glucose sensor, alerting the liver to high glucose intake in the diet. Because of the role insulin which plays in the natural physiology of glucose control, combined with suggestions that oral insulin may be

able to reverse insulin resistance[2,8], this treatment may be expected to maintain activity in patients with T2DM under circumstances where the efficacy of most, if not all, other medications wanes over time. For all these reasons, it is clear that oral insulin has a role to play in therapy for type 2 diabetes mellitus, and may be a candidate for the drug of choice in future treatment this disease.

Declaration of Interest:

The author is a co-founder and Chief Scientific Officer of Diabetology Ltd, one of the companies mentioned in this article, which is pursuing the commercial development of an oral insulin. The ideas and opinions expressed here are the author's own.

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