20 March 2014
EMA/CHMP/805158/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Victoza

International non-proprietary name: liraglutide

Procedure No. EMEA/H/C/001026/II/0023

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 7 August 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Victoza	liraglutide	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.7, 4.8 and 5.1 of the SmPC in order to include information on the use of liraglutide in combination with basal insulin. The Package Leaflet was proposed to be updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	7 August 2013
Start of procedure:	25 October 2013
Rapporteur's preliminary assessment report circulated on:	20 December 2013
Rapporteur's updated assessment report circulated on:	21 January 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 January 2014
MAH's responses submitted to the CHMP on:	13 February 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	4 March 2014
Rapporteur's final assessment report on the MAH's responses circulated on:	14 March 2014
CHMP opinion:	20 March 2014

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0003/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0003/2013 was not yet completed as some measures were deferred.

2. Scientific discussion

2.1. Introduction

Victoza (liraglutide) is a once-daily human glucagon-like peptide-1 (GLP-1) analogue. Compared to human GLP-1, liraglutide has a C16 fatty (palmitic) acid chain attached at position 26 (lysine) of the peptide, and has a lysine at position 34 replaced by an arginine. When administered subcutaneously (s.c.), these structural modifications result in pharmacokinetic (PK) properties of the compound suitable for once daily administration. Mode of action trials in subjects with type 2 diabetes mellitus (T2DM) have demonstrated glucose lowering, increased insulin secretion, restored beta-cell responsiveness to increasing glucose concentrations and delayed gastric emptying after a single s.c. dose of liraglutide.

EU approval for Victoza was obtained on 30 June 2009 for combination therapy with metformin, sulphonylureas (SUs), metformin and an SU or metformin and a thiazolidinedione (TZD), when the single or double agents did not result in adequate glycaemic control in patients with type 2 diabetes mellitus.

The application concerns a Type 2 variation for Victoza (Liraglutide). The MAH seeks to extend the indication in combination with basal insulin and to simplify the Victoza indication wording.

2.2. Clinical Pharmacology aspects

2.2.1. Methods – analysis of data submitted

The IDegLira clinical pharmacology programme assessed to what extent IDeg and liraglutide affect each other's pharmacokinetic profile in the IDegLira fixed ratio combination product. This was investigated in Trial **NN9068-3632**, a single-dose multi-period cross-over trial in healthy men, comparing IDegLira with the monocomponents IDeg and Lira. This trial was included in the MAA for IDeg, and also in the MAA for IDegLira. The dose tested was 17U/0.6mg, both as combination and as individual agents. The dose was based on the recommended starting dose of monocomponent Lira. The trial also included a period when IDeg and Lira were administered together as monocomponent formulations. Each subject was dosed on 4 occasions (IDegLira, IDeg, liraglutide and separate simultaneous administration of IDeg and liraglutide in randomized order) with 7-15 days wash-out in between. All doses were administered sc in the thigh. A 24 hour euglycaemic clamp was applied, and blood sampling for pharmacokinetic assessment was performed for 72 hours for liraglutide and 96 hours for IDeg.

2.2.2. Results

The bioavailability of IDeg was very similar when administered alone or in the combination, with a relative bioavailability of 103% (post-hoc 90% CI 0.99-1.07) and the C_{max} was somewhat higher after administering the combination, Cmax ratio of 1.12 (0.99-1.27). The relative bioavailability ($AUC_{0-\infty,IDeg,SD}$) for IDeg administered as part of IDegLira versus IDeg administered concomitantly with liraglutide was 0.98 $[0.95 ; 1.02]_{90\% CI}$, and the ratio of $C_{max,IDeg,SD}$ was 1.04 $[0.92 ; 1.18]_{90\% CI}$.

Liraglutide, on the other hand, showed a somewhat lower bioavailability when given in the combination, with an AUC ratio of 0.89 (post-hoc 90% CI 0.82-0.96), and a lower C_{max} (ratio 0.77, 90% CI 0.68-0.87). The relative bioavailability (ratio of $AUC_{0-\infty,lira,SD}$) for liraglutide administered as part of IDegLira versus liraglutide administered concomitantly with IDeg was 0.89 $[0.83 ; 0.97)]_{90\% CI}$, and the ratio of $C_{max,lira,SD}$ was 0.74 $[0.66 ; 0.84]_{90\% CI}$, indicating an 11% lower AUC and a 26% reduction in C_{max}. These observed

differences between the pharmacokinetics of IDegLira and liraglutide are not considered to impact the validity of the supportive evidence for combined use of IDeg and liraglutide obtained with IDegLira.

2.2.3. Discussion

As the interaction study was already assessed during other procedures, no full assessment was conducted in this procedure. The results of the submitted study show that the pharmacokinetics of IDeg are not influenced by concomitant administration of Lira alone or in any combination with IDeg. The 90% confidence intervals are within the acceptance criteria for bioequivalence.

With respect to the pharmacokinetics of Lira, the extent of absorption is not affected but the rate of absorption after administration of the combination product with IDeg is statistically significant decreased.

However, this lower Cmax of 26% is considered not clinical relevant.

2.3. Clinical Efficacy aspects

2.3.1. Methods – analysis of data submitted

In support of the application, four clinical trials were submitted (Table 1): Trial 3948 from the IDeg phase 3b programme, Trials 3697 and 3912 from the IDegLira phase 3a programme, and Trial 1842 from the liraglutide phase 3b programme. In these trials, IDeg and liraglutide were administered either as separate injections of the two individual drugs or as one injection of the fixed ratio combination product IDegLira in subjects with T2DM inadequately controlled on OADs, basal insulin in combination with OADs, or a GLP-1 receptor agonist in combination with OADs. Trial 3697 and 3912 were submitted with the MAA for IDegLira; trial 3948 was also submitted with the MAA for IDegLira, but as supportive study; trial 1842 was submitted in Type 2 variations for liraglutide and in for insulin detemir and has been assessed in those procedures.

The MAH considers trial 3948 as pivotal, while the other studies are seen as supportive.

Table 1: Overview of relevant clinical trials

Trial ID	Treatment	Trial duration	Antidiabetes treatment at screening	No. of subjects randomised	Random isation ratio
NN1250-3948 (key data)	IDeg+Lira+met vs. IDeg+IAsp+met	26 wks	IDeg+met	IDeg+Lira: 88 IDeg+IAsp: 89	1:1
NN9068-3697 (supportive data)	IDegLira+met±pio vs. IDeg+met±pio or Lira+met±pio	26 wks +26 wks extension	met ± pio (insulin-naïve)	IDegLira: 834 IDeg: 414 Lira: 415	2:1:1
NN9068-3912 (supportive data)	IDegLira+met vs. IDeg+met	26 wks	Basal insulin (IDet or IGlar) + met ± SU/ + met ± glinides	IDegLira: 207 IDeg: 206	1:1
NN2211-1842 (supportive data)	IDet+Lira+met vs. Lira+met	12 wks run-in, 26 wks +26 wks extension	met ± SU (insulin-naïve)	IDet+Lira: 162 Lira: 161	1:1

IAsp: insulin aspart; IDeg: insulin degludec; IDet: insulin detemir; IDegLira: insulin degludec/liraglutide combination product; IGlar: insulin glargine; Lira: liraglutide; met: metformin; pio; pioglitazone; SU: sulphonylurea; wks: weeks

2.3.2. Main study

Study 3948

This trial was a 26-week randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing the efficacy and safety of adding liraglutide versus addition of IAsp to IDeg OD + metformin. Eligible subjects were patients with type 2 diabetes who had completed approximately 104 weeks of treatment with IDeg + metformin in NN1250-3579 and the extension trial, NN1250-3643, with an end of treatment HbA1c ≥7.0%, thus qualifying for treatment intensification. Subjects were randomised 1:1 to add liraglutide once daily or IAsp with the largest meal as intensification of current treatment with IDeg OD + metformin.

A third treatment arm consisted of non-randomised subjects who completed NN1250-3643 and achieved the glycaemic target of HbA1c <7.0% at end of treatment. These subjects continued treatment with IDeg OD + metformin in order to further evaluate the long-term sustainability of glycaemic control. No comparisons were made between the non-randomised and the randomised treatment arms.

At randomisation, subjects in the IDeg + IAsp group were to start IAsp at 4U once daily with the largest meal and continue the IDeg dose they received prior to randomisation. In the IDeg + Lira group, subjects were to reduce their IDeg dose by 20% at randomisation and maintain this dose until Visit 8. Subjects in the IDeg + Lira arm started liraglutide at 0.6 mg/day and increased to 1.2 mg/day after one week. At Visit 7, liraglutide was to be increased to 1.8 mg/day if warranted based on the mean of three pre-breakfast SMPG values ≥ 5 mmol/L (90 mg/dL) measured just prior to Visit 7. In the subsequent 26 weeks of treatment, the subject's insulin dose was titrated once weekly based on self-measured plasma glucose (SMPG) to ensure the enforced titration towards a predefined glycaemic target.

The primary objective of the study was to compare the efficacy of adding liraglutide versus adding IAsp to the largest meal on top of IDeg (OD) + metformin in controlling glycaemia. The secondary objective was to compare the safety of adding liraglutide versus adding IAsp to the largest meal on top of IDeg OD + metformin.

The objective of the non-randomised arm was to evaluate the durability of IDeg to maintain glycaemic control over an additional 26 weeks in subjects who achieved the target HbA1c < 7% after 104 weeks of treatment with IDeg + metformin in NN1250-3579 and the extension trial, NN1250-3643.

Primary efficacy endpoint was change from baseline in HbA1c after 26 weeks of treatment using an analysis of variance (ANOVA) method with treatment, sex and region as fixed factors and age and baseline HbA1c as covariates. Secondary endpoints included HbA1c responders (HbA1c < 7%), responders without hypoglycaemia, responders without hypoglycaemia and weight gain, FPG, 9-point profile (SMPG), IDeg dose, body weight.

2.3.3. Supportive studies

For this Application three trials were submitted as supportive trials: trial 3697, 3912 and 1842. As stated above, trials 3697 and 3912 were submitted with the MAA for IDegLira. Both trials investigated the efficacy and safety of IDegLira. Trial 3697 was performed in insulin-naive subjects, while trial 3912 included patients failing on insulin+OADs. Therefore, study 3912 is considered more relevant for showing efficacy than trial 3697.

Trial 1842 was submitted in type 2 variation procedures for liraglutide and insulin detemir and has been assessed in those procedures. At that time, for addition of liraglutide to ongoing insulin therapy this study was considered inappropriate, as the trial investigated the effects of addition of insulin to ongoing liraglutide treatment. For the current Application the study has no value for efficacy but may be supportive for safety. It is mentioned briefly in this section.

Methods

Trial 3697

Trial 3697 was a randomised, controlled, parallel three-arm, multicentre, multinational treat-to-target trial with a 26-week main phase, which was followed by a 26-week extension phase to provide evidence of persistence of efficacy and safety during long-term exposure. The trial included subjects with type 2 diabetes inadequately controlled on metformin or metformin + pioglitazone, defined as HbA1c level of 7.0−10.0% (both inclusive). Subjects continued on their pre-trial OAD regimen throughout the duration of the trial. Primary objective was to confirm the efficacy of IDegLira in controlling glycaemia in subjects with type 2 diabetes. This was done by determining if the effect (change in HbA1c) of IDegLira was non-inferior to that of IDeg and superior to that of liraglutide after 26 weeks of treatment.

Trial 3912

Trial 3912 was a randomised, controlled, double-blind, parallel two-arm, multicentre, multinational, treat-to-target trial of 26 weeks duration. The trial included patients inadequately controlled on 20-40 units/day of basal insulin and 1-2 OADs (metformin, or metformin and sulfonylurea/glinides), defined as HbA1c of 7.5–10.0% (both inclusive). Primary objective was to confirm superiority of IDegLira vs. IDeg in controlling glycaemia in subjects with type 2 diabetes. The maximum insulin dose in the IDeg treatment arm was 50 units (i.e., equivalent to the insulin dose administered with the proposed maximum dose of IDegLira) in order to specifically assess the contribution of the liraglutide component to glycaemic control with IDegLira.

2.3.4. Results

Main study 3948

Participant flow

Of the 659 subjects who completed NN1250-3643, 413 patients were enrolled in/ randomised in NN1250-3948. A total of 88 patients were randomised to the IDeg + Liraglutide arm and 89 patients were randomised to the IDeg + IAsp arm. The remaining 236 patients were enrolled in the non-randomised arm. About 85 % of the patients completed the randomised part of the study.

Baseline data

Demographics, baseline and diabetes characteristics were generally similar between the treatment groups (Table 2). However, there was a slight imbalance in sex between treatment groups (more females in the IDeg + IAsp group). Most subjects were White (91%). Mean age was 61 years, mean HbA1c 7.7%, mean BMI 32.2 kg/m^2. Duration of treatment was 12.4 years.

Table 2: Demographics and Baseline Characteristics in study 3948, Full analysis set

	IDeg + Lira	IDeg + IAsp	Total
Number of Subjects	88	89	177
Age (years)	61.1 (9.5)	60.9 (8.8)	61.0 (9.2)
Sex			
Female	25 (28.4)	36 (40.4)	61 (34.5)
Male	63 (71.6)	53 (59.6)	116 (65.5)
Race			
White	79 (89.8)	83 (93.3)	162 (91.5)
Black or African American	6 (6.8)	3 (3.4)	9 (5.1)
Other	3 (3.3)	3 (3.4)	3 (3.4)
Body Weight (kg)	95.4 (19.2)	91.3 (16.8)	93.3 (18.1)
BMI (kg/m^2)	32.5 (5.4)	32.0 (4.8)	32.2 (5.1)
Duration of Diabetes (years)	12.9 (6.4)	11.8 (6.5)	12.4 (6.4)
HbA1c (%)	7.7 (0.6)	7.7 (0.8)	7.7 (0.7)
FPG (mmol/L)	6.4 (2.4)	6.1 (1.7)	6.3 (2.1)

Endpoints

The estimated mean reduction in HbA1c during the trial was −0.73 %-points with IDeg + Lira and −0.40 %- points with IDeg + IAsp, with a statistically significant estimated mean difference in favour of IDeg + Lira of −0.32 %−points [−0.53; −0.12]95%CI. After 26 weeks of treatment, the observed mean (SD) HbA1c was 7.0 (0.8) % with IDeg + Lira and 7.3 (0.8) % with IDeg + IAsp.

Secondary endpoints were in line with these results. Proportion of responders was larger for the IDeg + Lira group (58.0% vs 44.9%) and also the proportion of responders without hypoglycaemia was in favour of IDeg + Lira (54% vs 19%). In addition IDeg + Lira was accompanied with a decrease in body weight

of 3 kg vs no change in the IDeg + IAsp group. An overview of key results of this study is shown in **Error! Reference source not found.**.

Table 3: Key endpoints of study 3948

	IDeg + Lira	**IDeg + IAsp**
Number of Subjects	88	89
HbA1c change from baseline	-0.73%	-0.40%
Responders HbA1c< 7%	58.0% (51/88)	44.9% (40/89)
Responders for HbA1c without hypo's	54.3% (44/81)	19.3% (16/83)
Responders for HbA1c without hypo's and without weight gain	49.4%	7.2%
FPG (mmol/L)	-0.12	-0.18
Body weight (kg) change from baseline	-3.03	+0.72

Supportive studies

In **trial 3697**, withdrawal rates were generally low, although slightly higher in the liraglutide treated group. In this group more patients withdrew due to AEs. Baseline demographic characteristics were well balanced between groups as were the baseline diabetes characteristics. Mean diabetes duration was relatively short as could be expected in an insulin naïve group of patients with T2DM, but the range was very wide. All patients were on metformin treatment at inclusion and about 17 % were on concomitant pioglitazone treatment.

In **trial 3912**, withdrawal rates were balanced between groups as was the reasons for withdrawal. Baseline demographic characteristics were well balanced between groups as were the baseline diabetes characteristics. Mean diabetes duration was rather long as could be expected in an insulin treated group of patients with T2DM, but the range was very wide. About 50 % of patients were on dual OAD treatment at inclusion.

Key efficacy results from trial 3697 and 3912 are shown in Table 4 and results for hypoglycaemia in **Table 5**.

Table 4: Key efficacy results from Trial 3697 and 3912 after 26 weeks of treatment

	Trial 3697 (insulin naïve)			**Trial 3912 (insulin treated)**	
	IDegLira (N=833)	**IDeg (N=413)**	**Lira N=414)**	**IDegLira (N=199)**	**IDeg N=199)**
HbA1c (%)					
Baseline	8.3	8.3	8.3	8.7	8.8
Week 26	6.4	6.9	7.0	6.9	8.0
Change	-1.91	-1.44	-1.28	-1.90	-0.89

	Trial 3697 (insulin naïve)			**Trial 3912 (insulin treated)**	
IDegLira - IDeg	-0.47 [-0.58 ; -0.36]			-1.05 [-1.25 ; -0.84]	
IDegLira - Lira	-0.64 [-0.75 ; -0.53]				
Responders (%)					
HbA1c <7%	80.6	65.1	60.4	60.3	23.1
HbA1c <6.5%	69.7	47.5	41.1	45.2	13.1
Mean daily insulin dose (units)					
after 26 weeks	38	53	43	45	45
FPG (mmol/L)					
Baseline	9.2	9.4	9.0	9.7	9.6
Week 26	5.6	5.8	7.3	6.2	7.0
Change	-3.62	-3.61	-1.75	-3.46	-2.58
Mean 9-point profile post prandial increment (across all meals) (mmol/L)					
Baseline	2.3	2.6	2.5	2.5	2.3
Week 26	1.9	2.4	1.9	2.2	2.4
Change	-0.4	-0.2	-0.6	-0.3	+0.1
Body weight (kg)					
Baseline	87.2	87.4	87.4	95.4	93.5
Week 26	86.7	89.0	84.4	92.7	93.5
Change	-0.5	+1.6	-3.0	-2.7	0.0

Table 5: Overview of hypoglycaemic episodes – trial 3697 – safety analysis set

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	825				412				412			
Confirmed	263	(31.9)	699	180.2	159	(38.6)	496	256.7	28	(6.8)	41	22.0
Severe	2	(0.2)	2	0.5	2	(0.5)	2	1.0	0	(0.0)	0	0.0

Noct. confirmed	53	(6.4)	87	22.4	34	(8.3)	54	27.9	5	(1.2)	5	2.7
Severe	1	(0.1)	1	(0.3)	0	(0.0)	0	0.0	0	(0.0)	0	0.0

In both trials in the IDegLira group HbA1c decreased by 1.90% (from baseline HbA1c of 8.3 and 8.7%). IDegLira was superior to IDeg and Lira therapy. Results were supported by effects on FPG and prandial increments (both reduced). For the pre-defined glycaemic targets of HbA1c <7% and ≤6.5%, the proportion of IDegLira-treated subjects reaching targets were 80% and 70% (trial 3697), and 60% and 45% (trial 3912).

The results of the extension phase of trial 3697 show that the improvement in overall glycaemic control with IDegLira relative to comparators was maintained. Positive or neutral effects on body weight were also seen.

Hypoglycaemia was evaluated as an integrated part of efficacy and was a confirmatory secondary endpoint of trial 3697. In trial 3697 IDegLira had a lower risk of hypoglycaemia relative to IDeg. The risk relative to liraglutide was higher; however glycaemic control with liraglutide was less tight.

In trial 3912, hypoglycaemia rates were similar between IDegLira and IDeg. However, there was a greater improvement of HbA1c with IDegLira compared to IDeg.

Study 1842

Study 1842 was performed in T2DM patients to investigate the efficacy and safety of adding basal insulin detemir to the combination therapy liraglutide 1.8 mg+metformin. The purpose of the trial was to determine whether the effect of insulin detemir in combination with liraglutide 1.8 mg and metformin was superior to that of liraglutide 1.8 mg and metformin alone. patients inadequately controlled by Metformin (≥1500 mg daily) or Metformin + low dose SU (≤ half maximum dose) were switched to Metformin (same dose) + Liraglutide 1.8 mg daily. Subjects not adequately controlled after 12 weeks were randomised to receive insulin detemir as add-on to Metformin + Liraglutide or continued on Metformin + Liraglutide. Addition of insulin to liraglutide + metformin demonstrated a favourable, clinically relevant effect on the blood glucose control in terms of HbA1c reduction. The reduction in HbA1c in the triple therapy group at week 26 was (LS mean changes) -0.51%, vs. +0.02% in the metformin + liraglutide group (difference -0.52 [CI: -0.68; -0.36]). The estimated proportions of subjects achieving HbA1c both <7% and ≤6.5% were significantly greater with insulin detemir + liraglutide 1.8 mg + metformin (44% and 19%) compared to liraglutide 1.8 mg + metformin (20% and 7%). Improvements in other endpoints of glucose control were observed, including mean change in FPG and changes in post-prandial glucose levels.

Limitation of the study was that it only gives information about the efficacy and safety of insulin detemir when added to metformin + liraglutide. A treatment arm of insulin detemir + metformin was missing in Study 1842. Therefore, the impact of liraglutide itself in this triple therapy was not known. Triple therapy might have an advantage over combination treatment with metformin and insulin alone in terms of lower insulin dosage, fewer hypoglycaemic episodes and less weight gain, while achieving the same level of glucose control. However, this was not studied in this trial.

2.3.5. Discussion

In support of this application, the MAH has submitted four clinical trials: one pivotal (study 3948), and three supportive trials (3697, 3912 and 1842). Trial 3697 and 3912 were submitted as main studies with the MAA for IDegLira; trial 3948 was also submitted with the MAA for IDegLira, but as supportive study; trial 1842 was submitted in type 2 variation procedures for liraglutide and for insulin detemir and was assessed in those procedures.

Design and conduct of clinical studies

The **main clinical study (3948)** was a 26-week randomised, controlled, open-label, treat-to-target trial comparing the efficacy and safety of adding liraglutide versus addition of IAsp with the largest meal to IDEG + metformin. Eligible subjects were patients with type 2 diabetes who had completed approximately 104 weeks of treatment with IDeg + metformin in NN1250-3579 and the extension trial, NN1250-3643, with an end of treatment HbA1c ≥7.0%, thus qualifying for treatment intensification. Subjects were randomised 1:1 to add liraglutide once daily or IAsp with the largest meal to their current treatment with IDeg OD + metformin. The population of this study is a selected population who participated in trial 3579 for 52 weeks and in the extension trial 3643 for 52 weeks, before inclusion in this trial and as such they might not be as representative for the real clinical setting. In addition, as these patients are still qualifying for intensification of therapy, it is unlikely that IAsp administered once daily with the main meal will induce optimal glycaemic control. It can be expected that these subjects will need multiple daily injections.

In total 413 patients were enrolled/randomised of whom 88 received IDeg + Liraglutide and 89 IDeg + IAsp. The remaining 236 patients were enrolled in a non-randomised arm, the objective of which does not contribute to this application. Therefore, the sample size for this application is considered limited.

From the supportive studies, **trial 3912** is considered the most representative for this application, as it was conducted in subjects failing on basal insulin + OADs. The Applicant considers this study as supportive because IDegLira was used and not the separate components. It was a 26-weeks randomised, parallel, two-arm, double-blind, multi-centre, multinational, treat-to-target trial comparing IDegLira with IDeg in subjects with type 2 diabetes inadequately controlled with basal insulin and metformin with or without SU or glinides. Eligible subjects were randomised 1:1 to 2 treatment arms consisting of once daily IDegLira or once daily IDeg both in combination with metformin. The maximum dose of IDeg was limited to 50 units. This creates an artificial situation, but was done to enable an evaluation of the contribution of the liraglutide component to glycaemic control. Total number of subjects in this study was 398, which is considered acceptable.

Trial 3697 was conducted in subjects failing metformin ± pioglitazone. Subjects were randomised to receive IDegLira, Ideg or Lira in addition to their current treatment. Thus, the study population differs from the target population for this application. In addition, subjects received 2 medicines in addition to their current treatment, while normally one drug will be added. In addition, subjects in the IDegLira group started with a low dose of liraglutide (0.36mg) compared to the recommended starting dose of 0.6mg for Liraglutide as separate component. This might have influenced safety, in particular GI-side effects, in favour of IDegLira. Thus, data from this trial might not be generalised to a population failing on insulin + OADs who start with Liraglutide 0.6mg.

Trial 1842 investigated the effects of adding insulin to subjects failing on liraglutide + metformin. This study has been assessed before in 2 Type 2 variations (for liraglutide and insulin detemir). The limitation of this study was that it only gives information about the efficacy and safety of insulin detemir when added to metformin + liraglutide. The impact of liraglutide itself in this triple therapy was not demonstrated. The trial might have supportive value for safety aspects.

Efficacy data and additional analyses

In the **main clinical trial 3948** addition of liraglutide resulted in a mean reduction in HbA1c of -0.73% compared to -0.40% with addition of IAsp. The difference was statistically significant in favour of IDeg + Lira (mean difference -0.32 [95% CI: -0.53;-0.12]). It should be taken into account that HbA1c was intermediately high at baseline (7.7%). When compared to IDeg + IAsp, more patients reached the target criteria and did so with less hypoglycaemias, although the figures given by the MAH are somewhat flattered as for this analysis only subjects were included who completed the last 12 weeks of the study. A reduction in body weight was seen with IDeg + Lira: -3.03 kg with IDeg + Lira vs +0.72 Kg with IDeg + IAsp. Data from this trial indicate that the addition of liraglutide in patients failing on insulin + metformin can be effective. However, the comparison with IAsp was not quite valid, as it can be assumed that once daily dosing of IAsp might not be optimal in these patients. On the other hand, the reduction in hypoglycaemias is in favour of liraglutide.

Trial 3912 showed a treatment difference between IDegLira and IDeg (Max dose 50 units) of about 1% reduction in HbA1c. This difference is attributable to liraglutide, and thus these results are in favour of the addition of liraglutide in patients failing on insulin + metformin. The fact that the fixed ratio combination IDegLira was used in this study instead of IDeg + Lira is not considered a main issue, as pharmacokinetics of the fixed dose are similar to those of the separate components.

Trial 3697 showed superiority of IDegLira over IDeg and Lira when added to metformin. However, these results do not contribute to the claimed indication.

Trial 1842 does not contribute either to the claimed indication.

2.3.6. Conclusions on the clinical efficacy

Trial 3948 and trial 3912 indicate that liraglutide might be effective in subjects not sufficiently controlled by insulin + metformin. However, the number of subjects in the main trial (3948) was limited.

2.4. Clinical Safety aspects

The safety data from the four clinical trials were not pooled due to differences in study design. All trials had a follow-up duration of 26 weeks and trial 3697 and 1842 had an extension period of 26 weeks and these extension periods were also used for the clinical safety analysis.

Two analysis sets were used for the safety evaluation, as defined below:

- **Safety analysis set (SAS)**: includes subjects receiving at least one dose of the investigational medicinal product or comparators. Subjects in the safety analysis set were contributed to the evaluation 'as treated'.
- **Full analysis set (FAS):** all randomised subjects in the trial. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised". In Trial 1842 only subjects with at least one efficacy value after the randomisation visit were included in the FAS.

2.4.1. Methods – analysis of data submitted

Patient exposure

In **Table 6** patient exposure is shown in the four different trials.

Table 6. Exposure to IDeg+liraglutide, IDegLira or IDet+liraglutide across the trials 3948, 3697, 3912, 1842-SAS

	Trial 3948	Trial 3697ext	Trial 3912	Trial 1842ext
Trial duration	26 weeks	26+26 weeks	26 weeks	26+26 weeks
Number of subjects exposed	IDeg + liraglutide N = 87	IDegLira N = 825	IDegLira N = 199	IDet + liraglutide N = 163
Exposure in subject years	40.04	705.6	91.93	144.5

N: number of subjects, ext: extension, IDeg: insulin degludec, IDegLira: insulin degludec + liraglutide, IDet: insulin detemir

In Trial **3948**, mean average daily dose IDeg was 0.65 U/kg in the IDeg + Lira and 0.64 U/kg in the IDeg + IAsp arm. Concerning liraglutide, 2 (2.3%) subjects were taking liraglutide 0.6 mg/day, 28 (32.2%) were taking 1.2 mg/day and 57 (65.5%) were taking 1.8 mg/day.

In trial **3679**, mean average daily insulin dose was 31.0 units/day in the IDegLira group compared to 36.9 units/day in the IDeg group. The mean average daily liraglutide dose in the IDegLira group was 1.1 mg/day compared to 1.7 mg/day in the liraglutide group.

In trial **3912**, mean average daily insulin dose was 38.2 units/day in the IDegLira group compared to 38.6 units/day in the IDeg group.

In trial **1842**, subjects were exposed to 1.8 mg liraglutide and a mean average daily dose of 39.8 IU IDet in the IDet+liraglutide group.

2.4.2. Results

Adverse events

For trial **3948**, number of adverse events and their severity is shown in

Table 7. The combined use of IDeg with liraglutide led to a higher rate of adverse events compared to IDeg used with IAsp (517/100 PY vs 274/100 PY respectively). In total 62.4% of all subjects reported 318 events in trial **3948**. The observed rate of adverse events was 517 events per 100 PYE in IDegLira group and 274.1 events per 100 PYE in the IDeg group. Most events were of mild severity.

The most frequently reported AEs in the IDeg + liraglutide treatment group were nausea (reported by 20.7% of the subjects), diarrhoea (10.3% of the subjects) and nasopharyngitis (10.3% of the subjects). The most frequently reported AE in the IDeg + IAsp treatment group was nasopharyngitis, reported by 12.8% of the subjects. The differences in adverse events in the IDeg + liraglutide group compared to the IDeg + IAsp group were mainly caused by more gastro-intestinal adverse events, as expected from liraglutide, and this was also observed in the IDegLira Trials 3697 and 3912 and in Trial 1842 (IDet + liraglutide). No new types of adverse events were reported for the combined use of IDeg + liraglutide.

Table 7. Adverse events-treatment emergency-Trial 3948

	IDeg + Liraglutide N (%) E R	IDeg + IAsp OD N (%) E R	Total N (%) E R
Number of Subjects	87	86	173
Events	61 (70.1) 207 517	47 (54.7) 111 274	108 (62.4) 318 395
Serious			
Yes	4 (4.6) 4 10	5 (5.8) 5 12	9 (5.2) 9 11
No	60 (69.0) 203 507	45 (52.3) 106 262	105 (60.7) 309 384
Severity			
Severe	5 (5.7) 6 15	4 (4.7) 4 10	9 (5.2) 10 12
Moderate	24 (27.6) 46 115	16 (18.6) 24 59	40 (23.1) 70 87
Mild	56 (64.4) 155 387	40 (46.5) 83 205	96 (55.5) 238 296
Outcome			
Recovered	59 (67.8) 165 412	36 (41.9) 70 173	95 (54.9) 235 292
Recovering	0 (0.0) 0 0	2 (2.3) 3 7	2 (1.2) 3 4
Recovered with Sequelae	0 (0.0) 0 0	1 (1.2) 1 2	1 (0.6) 1 1
Not Recovered	27 (31.0) 42 105	21 (24.4) 37 91	48 (27.7) 79 98

N= Number of Subjects
%= Percentage of Subjects
E= Number of Events
R= Event Rate per 100 Patient Years of Exposure

In Trial **3697**, the percentage of subjects reporting AEs during the first 26-week treatment period was 63.2%, 60.2% and 72.6%, for IDegLira, IDeg and Lira respectively with corresponding rates 482.8 and 430.0 and 640.5 events per 100 PYE

The AE rates over the 52-week period were 407.9, 383.3 and 507.3 events per 100 PYE for IDegLira, IDeg and Lira, respectively.

In **Trial 3912**, the percentage of subjects reporting AEs was similar for IDegLira (57.8%) and IDeg (61.3%). The rate of AEs in the IDegLira group (398.1 events per 100 PYE) was similar to the rate in the IDeg group (355.5 events per 100 PYE). Most AEs were mild or moderate in both treatment groups and the rate of severe AEs in the IDegLira group (7.6 events per 100 PYE) was similar to the rate in the IDeg group (8.9 events per 100 PYE).

In **Trial 1842**, the percentage of subjects reporting AEs during the entire trial (run-in to end of trial) was similar for the liraglutide group (78.0%) and the IDet + liraglutide group (81.0%). Most AEs were mild or moderate in both treatment groups and the percentage of subjects having severe AEs in the liraglutide group (8.8%) was similar to the IDet + liraglutide group (10.4%). Most AEs were assessed as unlikely related to trial product by the investigator in both treatment groups with no difference between the treatment groups.

According to the Applicant, the proportion of subjects with AEs for subjects treated with IDegLira or liraglutide + IDet were within the same range as the proportions of subjects with AEs in the IDeg + liraglutide group in Trial 3948: 70.1% in **Trial 3948**; 71.2% in **Trial 3697**; 57.8% in **Trial 3912** and 81.0 % in **Trial 1842**.

Serious adverse event/deaths/other significant events

Deaths

In **trial 3948** and **3912** no deaths were reported.

In trial **3697**, 2 treatment-emergent and 1 non treatment-emergent deaths were seen. All subjects were treated with IDegLira.

Trial **1842** reported 1 treatment-emergent death in the liraglutide group.

SAEs

There were 9 SAEs in the randomised arms of Trial **3948**: 4 in the IDeg + liraglutide group and 5 in the IDeg + IAsp group, corresponding to a rate of 10 and 12 events per 100 PYE. None of these were related to trial product as assessed by the investigator.

In the supportive trials the percentage of subjects with SAEs was low and in the same range as in Trial 3948. No pattern or clustering of events was observed during the trials, and no preferred terms were reported for more than 1% of the subjects. The most frequently reported SAEs were represented in the SOCs 'cardiac disorders', 'infections and infestations' and 'nervous system disorders'. 2 SAE`S hypoglycaemia were reported in 3697 and 1 in 3912.

Cardiovascular events

In all 4 trials, the numbers of MACEs were low and with no apparent difference in the rate of MACE reported by subjects treated with the combined used of IDeg and Lira (as a free or fixed ratio combination) compared to subjects treated with IDeg + IAsp or with the IDeg or Lira monocomponents. However, the numbers are very small and should be interpreted with caution.

In **3948**, one event was classified as a stroke in the IDeg +IAsp group.

In the pooled data from **Trials 3697 and 3912**, a total of 216 cardiovascular events reported for 167 subjects were identified based on the SMQ search. The rate of cardiovascular events was 13.7 events per 100 PYE in the IDegLira group, 14.3 for IDeg and 13.2 for liraglutide. The most frequently reported cardiovascular event in the search was 'oedema peripheral' with no difference among the treatment groups. The majority of cardiovascular events were mild or moderate, and the rate of severe cardiovascular events with IDegLira, IDeg and liraglutide was 0.9, 1.6 and 1.2 events per 100 PYE, respectively.

In Trial **1842**, 4 serious treatment-emergent cardiovascular events during the trial were identified: 2 in the liraglutide group (cardiac failure and angina) and 2 in the IDet + liraglutide group (coronary artery disease and angina). All events were assessed as unlikely related to trial treatment.

Pancreatitis

In the pivotal study **3948** a total of 12 TEAEs for 7 subjects were identified as pancreas-related. The rate of pancreas-related events was 27 events per 100 PYE with IDeg + liraglutide and 2 events per 100 PYE with IDeg + IAsp. One event of pancreatitis was reported for 1 person in the IDeg+IAsp OD group. Seven (7) events of 'lipase increased' were reported for 6 subjects (all in the IDeg + liraglutide treatment group); 4 of these subjects also reported events of 'amylase increased'. The increase in amylase and lipase in the IDeg+Liraglutide group, were not associated with pancreatitis.

In the pooled data from Trials **3697** and **3912**, 5 events of pancreatitis for 5 subjects were identified: 2 of these were confirmed by the external EAC as events of acute pancreatitis (1 with IDeg and 1 with Lira). No confirmed episodes of pancreatitis were reported with IDegLira.

In addition, 17 events of elevated lipase and/or amylase reported for 15 subjects were identified based on predefined criteria and sent to the external EAC for adjudication; 1 event of 'lipase increased' in the liraglutide group was confirmed to be acute pancreatitis by the EAC.

In **trial 1842,** 2 events of pancreatitis were reported in the liraglutide arm. In addition, increase in lipase was seen in 10-16% of subjects treated with liraglutide or IDet+Lira.

Neoplasms

The overall rates of neoplasms reported in the IDeg + liraglutide and IDegLira treatment groups were low and similar to those reported in the comparator groups in the four trials. The rates of malignant neoplasms were similar between IDeg + liraglutide and IDeg + IAsp and between IDegLira and IDeg.

In the pooled safety dataset **3697/3912** the neoplasm event rate was 3.3 per 100 PYE in the IDegLira group, 2.5 per 100 PYE in the IDeg group and 3.3 per 100 PYE in the liraglutide group.

Hypoglycaemia

Confirmed hypoglycaemic episodes consisted of episodes of severe hypoglycaemia as well as minor hypoglycaemic episodes with a confirmed PG value of less than 3.1 mmol/L (56 mg/dL).

In **trial 3948** no episodes of severe hypoglycaemia were observed. The percentage of subjects who experienced confirmed hypoglycaemic episodes during the treatment period was 27.6% in the IDeg + Lira group and 67.4% in the IDeg + IAsp group. The rate of confirmed hypoglycaemic episodes per 100 PYE was lower in the IDeg + Lira group compared with IDeg + IAsp (100 and 815 episodes per 100 PYE, respectively).

For the pooled trials **3697 and 3912,** a total of eight episodes of severe hypoglycaemia were reported. 4 episodes in the IDegLira groups, 2 in the liraglutide group and 2 in the IDeg group. In study **3697**, the percentage of subjects who experienced confirmed hypoglycaemic episodes during the first 26-week treatment period was 31.9% in the IDegLira group compared to 38.6% in the IDeg group and 6.8% for liraglutide. In Trial **3912**, the rate of confirmed hypoglycaemic episodes with IDegLira was 153.4 events per 100 PYE) and with IDeg 263.3 events per 100 PYE, although the proportion of subjects experiencing confirmed hypoglycaemic episodes were similar for IDegLira and IDeg (24.1% and 24.6%).

In trial **1842,** there were no severe episodes of hypoglycaemia in the randomized groups.

Laboratory findings

Apart from changes in lipase/amylase no clinically relevant changes in haematology and biochemistry parameters were observed from baseline to end of treatment in any of the treatment groups in all trials.

In all 4 trials, **amylase** and **lipase** values appeared unchanged by insulin treatment as seen in the IDeg + IAsp group of Trial 3948 and the IDeg groups of Trial 3697 and 3912. An increase in amylase and lipase values was observed in all 4 trials with liraglutide treatment (as liraglutide, IDegLira, IDeg + liraglutide and IDet + liraglutide). The increase in amylase and lipase values with liraglutide was not affected by concomitant treatment with insulin.

The proportion of subjects having lipase values above the reference range increased from appoximately 10% at baseline to approximately 30% in the IDeg + liraglutide group and 15% in the IDeg + IAsp group at Week 26 in trial 3948.

Immunological events

Few events of allergic reactions were reported for the main **Trial 3948** and the supportive Trials 3697 and 3912, and there was no difference among treatment groups. The majority of the events were not related to the trial products.

In the supportive trials 3697 and 3912, 5 and 8% of patients treated with IDegLira developed antibodies to human insulin or insulin degludec antibodies within 26-52 weeks after the start of treatment compared to 2and 3% for IDeg. None of these antibodies were shown to neutralize the activity of human insulin or insulin degludec. Few subjects developed anti-liraglutide antibodies (0.5-3% at different time points). Of these 5 (4 with IDegLira and 1 with liraglutide) were demonstrated to have an *in vitro* neutralising effect at Week 53 in trial 3697.

Safety in special populations

About one third of the subjects included in the pivotal trial were elderly subjects (> 65 years): 36.8% of the subjects in the IDeg + liraglutide group and 33.7% in the IDeg + IAsp OD group (**Table 8**). There was no indication of a higher rate of AEs in elderly subjects compared to adult subjects treated with IDeg + liraglutide. However, in both treatment groups, the rate of confirmed hypoglycaemia was lower in subjects aged 18-65 years.

In the supportive trials 3697 and 3912, no impact of age on AE rates was apparent. An analysis of intrinsic and extrinsic factors was not performed in trial 1842.

Table 8 Adverse events by age group –Trial 3948-SAS

	IDeg + liraglutide				**IDeg + IAsp od**			
	N	(%)	E	R	N	(%)	E	R
Safety analysis Set								
Age 18-65 years	55	(63.2)			57	(66.3)		
Age > 65 years	32	(36.8)			29	(33.7)		
Total Exposure (yrs)								
Age 18-65 years	25.2				26.9			
Age > 65 years	14.6				13.6			
All adverse Events								
Age 18-65 years	42	(76.4)	149	585.8	31	(54.4)	69	256.7
Age > 65 years	19	(59.4)	58	397.2	16	(55.2)	42	308.4
Hypoglycaemia confirmed								
Age 18-65 years	14	(25.5)	17	66.8	35	(61.4)	187	695.7
Age > 65 years	10	(31.3)	23	157.5	23	(79.3)	143	1050.1

N: number of subjects, E: number of events, R: number of events per 100 PYE (patient years of exposure)

Discontinuation due to adverse events

Approximately 5% of subjects in the 4 trials were withdrawn due to AEs. Apart from 'gastrointestinal disorders', no clustering in type of adverse event withdrawals was observed and no treatment group difference was apparent with respect to number of subject withdrawals due to adverse events.

Post marketing experience

The post marketing experience with Tresiba is currently very limited. Tresiba was launched in the United Kingdom on 28 January 2013, in Denmark on 04 March 2013, in Japan on 07 March 2013, in Mexico on 21 May 2013 and in Switzerland 04 June 2013.The first periodic safety update report for Tresiba was submitted on 03 June 2013.

No safety signal has emerged when Victoza is used in combination with insulin compared to the signals reported with the separate use of the products based on spontaneous AEs reporting. No new significant information on drug interactions, drug abuse or misuse, experiences during pregnancy or lactation, experience in special patient groups or on the effects of long-term treatment was received during the reporting period for Victoza (cut-off 30 December 2012).

2.4.3. Discussion

Safety data were presented from the four clinical trials. Data were not pooled due to differences in study design. A total of 1274 patients with type 2 diabetes have been exposed to a combination therapy with liraglutide and basal insulin (IDeg+liraglutide, IDegLira or IDet + liraglutide), of which 751 have been exposed for at least 52 weeks. All patients in the studies were exposed to liraglutide and basal insulin on a background therapy of metformin. In addition, in trial 3697, 17.0% were using a combination of metformin and pioglitazone.

The pivotal study 3948 is a relatively small study (N=87 for the IDeg + Lira arm) with a short study duration (26 weeks), not enough to prove safety. To conclude on safety, the data of the supportive studies are also of importance due to the higher number of subjects exposed to both liraglutide and insulin in the same period (N=825 in trial 3697 and N=621 completed the extension period)(N=199 in 3912 group)(N=163 in trial 1842 and N=130 completed the extension period). In trial 3697 and 3912 IDegLira was used in a fixed ratio combination, and therefore not completely comparable to the real life situation in which different dose combinations of insulin and liraglutide will be used. More experience with the combined use of IDegLira as well as IDet +liraglutide comes from the extension periods in trial 3697 and 1842 and the data assessed in this current application is considered as sufficient to assess short term safety. The safety analysis set is overall representative of a population of adult patients with T2DM, the majority of subjects had a mean diabetes duration > 5-10 years.

The most common adverse events associated with liraglutide and basal insulin are gastrointestinal side effects as expected due to the liraglutide component. In study 3948 the incidence for IDeg+Lira, IDeg+IAsp, respectively were; nausea (20.7 and 1.2%), diarrhoea (10.3 and 1.2%), vomiting (5.7 and 0%). In study 3697 the incidence for IDegLira, IDeg and Lira, respectively were; nausea (10.3, 3.9, 22.3 %), diarrhoea (10.2, 6.8, 16.3%), vomiting (5.0, 2.4, 9.2%).These adverse events have previously been shown to be related to the actual liraglutide dose and also to the rate of dose uptitration. Since the actual dose of liraglutide was lower in trial 3697 and the dose uptitration slower in the IDegLira compared to the Lira group, the lower incidence in the IDegLira group is an expected finding. Thus, GI data from IDegLira might not be generalised to a population failing on insulin + OADs who start with Liraglutide 0.6mg.

As expected, the incidence of hypoglycaemia was lower in the IDeg + Lira group compared to the IDeg + IAsp group in trial 3948. Rates of confirmed hypoglycaemia were slightly higher in the elderly in both treatment groups (IDeg + Lira >65yrs: 157.5, ≤65 yrs: 66.8; IDeg + IAsp >65 yrs:1050.1, ≤65 yrs:

695.7) but rates were lower in the IDeg + Lira group as compared to the IDeg + IAsp group. Also, in study 3697 the incidence of hypoglycaemia was lowest in the liraglutide group. The higher incidence for IDeg compared to IDegLira in that study is most likely due to the higher insulin dose. In study 3912 the incidences were similar in the two groups. In conclusion, there is no indication of an additive effect with respect to the risk of hypoglycaemia when IDeg is combined with Lira. However, there were 3 hypoglycaemia SAEs reported in patients on IDegLira in trial 3697 and 3912which should be further discussed.

The current safety data base is too small to draw conclusions with respect to cardiovascular safety of the combination of IDeg and Liraglutide. An increased pulse rate was observed with GLP-1 use, so the outcomes of the ongoing CV outcome studies are of clinical relevance.

There is limited experience of use of liraglutide and basal insulin in patients with congestive heart failure NYHA class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV.

The number of potential events of acute pancreatitis and pancreatic enzyme elevations was low and no confirmed episodes of pancreatitis were reported with combination of liraglutide and basal insulin therapy. Acute pancreatitis has been previously identified as a potential safety issues for the GLP-1 receptor agonist class. Acute pancreatitis is included in the RMP as important identified risk.

The incidence of allergic reactions seen in the IDeg+liraglutide treated group in the pivotal study was low, one subject had a possible reaction on liraglutide and withdrew. In the pooled safety analysis set of supportive trials 3697 and 3912 the incidence was low (0.9%) and numerically lower than for the other treatments. In the supportive trials 4.8% of patients treated with IDegLira had an increase in antibodies to human insulin or specific insulin antibodies to insulin compared to 1.9% of patients treated with IDeg. No neutralising insulin anti-bodies were detected. Few subjects developed anti-liraglutide antibodies (0.5-3% after 52 weeks treatment), 4 subjects treated with IDegLira had anti-bodies that were demonstrated to have an *in vitro* neutralising effect. Overall, antibody development has previously been detected for both liraglutide (8.6%) and IDeg.

GLP-1 receptor agonists have been associated with thyroid C-cells proliferative/hyperplasia in non-clinical carcinogenicity studies, but the relevance for humans is unsure. The current data base is too limited and the duration of the studies too short to provide any useful information about thyroid or other neoplasms. The potential tumour growth promoting effect of insulin analogues due to their anabolic properties is an ongoing discussion. However, no firm association has been established between any insulin analogues and increased cancer risk. Considering the findings of C-cell tumors in rats when given liraglutide, an additive effect on the risk of malignancies when combining Lira and Ideg could be hypothesised. However, this risk seems very remote and is not considered strong enough to justify a request for specific PAS studies. Long term PAS studies are ongoing for both Lira and IDeg which will provide more information about neoplasms. As a result of the recent art 5(3) procedure, pancreatic cancer should be included in the RMP as a potential risk. In the current clinical development program, one subject treated with liraglutide was diagnosed with metastatic pancreatic adenocarcinoma. No medullary thyroid cancer event was reported in any of the treatment groups.

The incidence of AEs were similar in patients below and above age 65 years. The number of subjects ≥ 75 years is very low.

Since all patients had a background therapy of metformin there is no clinical experience of liraglutide and basal insulin administered alone or in combinations with other oral antidiabetic drugs than metformin or a combination of metformin and pioglitazone. One-hundred-forty (140) patients were treated with IDegLira in combination with metformin+pioglitazone. There were no indications of increased incidence of adverse events in these patients.

2.4.4. Conclusions on clinical safety

The safety profile for IDegLira is in general similar to the two included mono-components with no indications of additive toxicity. Since the actual liraglutide dose in the studies was lower and the up-titration of dose somewhat slower the prevalence and severity of the well-known gastrointestinal side-effects were lower compared to liraglutide as monotherapy. No new safety issues have been identified for this combination. There are some issues that need further clarification, e.g. possible risk of mix-ups and medication errors.

With regard to the long-term safety, the initial cardiovascular safety evaluation is acceptable with a potentially beneficial effect on systolic blood pressure in contrast to slight increase in heart rate in the clinical studies. Otherwise, the long-term safety concerns are the same as for the other GLP-1 agonist and insulin analogues, i.e. identified risk of pancreatitis and potential risks of malignancies e.g. pancreatic and thyroid tumours.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

Section 4.1 of the SmPC

was amended to reflect the new combination with basal insulin. In addition to this the MAH simplified the indication for Victoza as follows.

Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with: oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations).

~~– Metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea.~~

~~In combination with:~~

~~– Metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.~~

Section 4.2 of the SmPC

was amended to reflect the combination with basal insulin as follows (similar additions were made to 4.4, 4.7):

[…]

Victoza can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy or a basal insulin. When Victoza is added to sulphonylurea therapy or basal insulin, a reduction in the dose of sulphonylurea or basal insulin should be considered to reduce the risk of hypoglycaemia (see section 4.4).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Victoza. However, when initiating treatment with Victoza in combination with a sulphonylurea or a basal insulin, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea or the basal insulin.

Section 4.4 of the SmPC

was amended to reflect that the data for the combination of liraglutide and insulin degludec is no longer missing.

[…]

Victoza is not a substitute for insulin.

~~The addition of liraglutide in patients already treated with insulin has not been evaluated and is therefore not recommended.~~

Section 4.8 of the SmPC

was amended to provide information on hypoglycaemic events as follows:

[…]

Hypoglycaemia

Most episodes of confirmed hypoglycaemia in clinical studies were minor. No episodes of major hypoglycaemia were observed in the study with Victoza used as monotherapy. Major hypoglycaemia may occur uncommonly and has primarily been observed when Victoza is combined with a sulphonylurea (0.02 events/subject year). Very few episodes (0.001 events/subject year) were observed with administration of Victoza in combination with oral antidiabetics other than sulphonylureas. The risk of hypoglycaemia is low with combined use of basal insulin and liraglutide (1.0 events per subject year, see section 5.1).

Section 5.1 of the SmPC

was amended to reflect the available data for the combination with insulin as follows:

[…]

Combination with insulin

In a 104-week clinical trial, 57% of patients with type 2 diabetes treated with insulin degludec in combination with metformin achieved a target HbA1c <7% and the remaining patients continued in a 26-week open label trial and were randomised to add liraglutide or a single dose of insulin aspart (with the largest meal). In the insulin degludec + liraglutide arm, the insulin dose was reduced by 20% in order to minimize the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA1c (-0.73% for liraglutide vs -0.40% for comparator) and body weight (-3.03 vs 0.72 kg). The rate of hypoglycaemic episodes (per patient year of exposure) was statistically significantly lower when adding liraglutide compared to adding a single dose of insulin aspart (1.0 vs 8.15; ratio: 0.13; 95% CI: 0.08 to 0.21).

Additional minor changes related to renaming of tables, and moving the paragraph regarding the combination of liraglutide with insulin detemir to the section on "Combination with insulin", were also made.

The package leaflet was amended accordingly as follows:

Section 1 - What Victoza is and what it is used for

[…]

Victoza is used with other medicines for diabetes when they are not enough to control your blood sugar levels. These may include:

oral antidiabetics (such as metformin, pioglitazone, sulphonylurea medicines) and/or a basal insulin, a type of insulin which works all day.~~to treat adults with type 2 diabetes mellitus when:~~

~~– metformin or a sulphonylurea alone (such as glimepiride or glibenclamide) despite the maximal tolerated dose are not enough to control your blood sugar levels.~~

~~– metformin in combination with a sulphonylurea (such as glimepiride or glibenclamide) or metformin in combination with a glitazone (such as pioglitazone) are not enough to control your blood sugar levels.~~

Section 2 - What you need to know before you use Victoza

In particular, tell your doctor, nurse or pharmacist if you are using medicines for diabetes containing any of the following active substances:

~~• Insulin. Victoza is not recommended if you are already using insulin.~~

• *Sulphonylurea (such as glimepiride or glibenclamide). You may get hypoglycaemia (low blood sugar) when using Victoza together with a sulphonylurea as sulphonylureas increase the risk of hypoglycaemia. When you first start using these medicines together, your doctor may tell you to lower the dose of the sulphonylurea medicine. Please see section 4 for the warnings signs of low blood sugar.*

Section 4 - Possible side effects

Serious side effects

Common: may affect up to 1 in 10 people

• *Hypoglycaemia (low blood sugar). The warning signs of low blood sugar may come on suddenly and can include: cold sweat, cool pale skin, headache, fast heart beat, feeling sick, feeling very hungry, changes in vision, feeling sleepy, feeling weak, nervous, anxious, confused, difficulty concentrating, shaking (tremor). Your doctor will tell you how to treat low blood sugar and what to do if you notice these warning signs. This is more likely to happen if you also take a sulphonylurea or a basal insulin.Your doctor may reduce your dose of these medicines before you start using Victoza.~~If you are already taking a sulphonylurea medicine when you start using Victoza, your doctor may tell you to reduce the dose of the sulphonylurea.~~*

2.6. Significance of paediatric studies

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0003/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0003/2013 was not yet completed as some measures were deferred.

3. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

In support of this application, the MAH has submitted four clinical trials: one pivotal (study 3948), and three supportive trials (3697, 3912 and 1842). Trial 3697 and 3912 were submitted with the MAA for IDegLira; trial 3948 was also submitted with the MAA for IDegLira, but as supportive study; trial 1842 was submitted in Type 2 variations for liraglutide and for insulin detemir and has been assessed in those procedures.

The pivotal study **3498** was a 26-week randomised, controlled study comparing the efficacy of liraglutide vs Insulin Aspart (IAsp) as add-on therapy in subjects insufficiently controlled by Insulin Degludec (IDeg) + Metformin In total, 177 subjects were randomised, 88 subjects were randomised to IDeg + Liraglutide and 89 to IDeg + IAsp once daily with the largest meal. IDeg and IAsp were titrated to target. IDeg dose was reduced by 20 % in the IDeg+liraglutide arm at baseline.

Study **3697** was a three-armed study (834 subjects in IDegLira group, 414 in Ideg group, 415 in liraglutide group) including insulin-naïve patients with inadequate metabolic control on metformin+/-pioglitazone. The duration of the study was 26 weeks and there was a 26 week extension period. In this study IDegLira, given at a maximum dose of 50 dose steps (50 units of IDeg and 1.8 mg liraglutide), was compared with IDeg which was titrated to target and liraglutide administered according to label. In the smaller study **3912** (26 weeks), IDegLira treatment (207 subjects) was compared with IDeg (206 subjects) given at a maximum dose of 50 units, thereby evaluating the contribution of the liraglutide component. Trial **1842** investigated the effect of adding IDet in insulin-naïve subjects with T2DM inadequately controlled on liraglutide and metformin after a run-in period of 12 weeks. The duration of the trial was 26 weeks and this trial had also an extension period of 26 weeks.162 subjects were included in the IDet + liraglutide arm and 161 in liraglutide arm.

The studies were generally well designed and conducted. The pivotal study was relatively small, trial 3697 included insulin-naïve patients and this is not in line with the claimed indication, add-on to subjects failing on insulin ± OADs. Study 3697 and 3912 investigated the fixed ratio combination IDegLira and are not completely comparable to the combined use of the separate monosupplements, especially with regard to the titration procedure. Trial 1842 investigated the effects of adding IDet to liraglutide, and not the efficacy of liraglutide. Therefore this trial does not contribute to the claimed indication.

The outcome of study **3948**, showed that the effect of IDeg + liraglutide on HbA1c reduction was superior to IDeg + IAsp once daily. HbA1c decreased by 0.74% with IDeg+liraglutide and by 0.39% with IDeg+IAsp. The difference was statistically significant. A total of 58.0% of subjects on IDeg + liraglutide achieved an HbA1c <7% compared to 44.9% with IDeg + IAsp (NS), while 54.3% and 19.3% achieved the target without confirmed hypoglycaemia (estimated odds ratio (IDeg + liraglutide / IDeg + IAsp): 5.57 [2.67; 11.63]95%CI). A total of 49.4% vs. 7.2% achieved this target without confirmed hypoglycaemia and weight gain (estimated odds ratio: 13.79 [5.24; 36.28]95%CI).

After 26 weeks of treatment, the mean daily IDeg dose in the IDeg + liraglutide group was 0.65 U/kg and 0.64 U/kg in the IDeg + IAsp arm. By Week 26, 32.2% of subjects treated with IDeg + liraglutide administered 1.2 mg/day and 65.5% administered 1.8 mg/day of liraglutide. The mean daily IAsp dose was 0.21 U/kg in the IDeg + IAsp arm.

Other secondary endpoints supported the primary outcome. The estimated mean change in FPG was comparable between treatments with an estimated treatment difference (IDeg+liraglutide – IDeg+IAsp) of 0.06 mmol/L [−0.65; 0.77]95%CI. Nine-point SMPG values improved in both groups. Prandial increments did not differ significantly between treatment groups. The observed change in body weight was -2.8 kg and 0.9 kg with IDeg + liraglutide and IDeg + IAsp, respectively, with an estimated treatment difference (IDeg+liraglutide – IDeg+IAsp) of -3.75 kg [-4.70; -2.79]95%CI.

The outcome of study **3697** showed that the effect of IDegLira on HbA1c reduction was superior to both the mono-components (HbA1c decreased by 1.91%with IDegLira, by 1.44% with IDeg and by 1.28% with liraglutide). The differences were statistically significant. Data from the extension study showed that this effect was maintained up to 52 weeks with only marginally increased doses of IDegLira. The reduction in HbA1c was also reflected in significantly higher responder rates with IDegLira, both when applying the HbA1c cut-off of 7 % (80.6 %) and the stricter cut-off of 6.5 % (69.7 %) compared to both mono-components (IDeg 65.1 % and 47.5 %; liraglutide 60.4 % and 41.1 %). Higher proportions of patients reached the responder target without experiencing hypoglycaemia or weight gain in the IDegLira group compared to IDeg treated subjects whereas no difference was observed compared to liraglutide.

Insulin doses were significantly lower in the IDegLira treated group compared to the IDeg treated group. At week 26 the mean insulin dose in the IDegLira group was 38 dose steps and 39.7% of subjects reached a daily insulin dose of 50 dose steps. In the IDeg groups the mean insulin dose was 53 units and 53.9 % of patients were on doses > 50 units.

Other secondary endpoints supported the primary outcome. A comparable effect on FPG was observed with IDegLira and IDeg (-3.62 mmol/L vs. -3.61 mmol/L, liraglutide -1.75 mmol/L), whereas the effect on post-prandial glucose increment was comparable for IDegLira and liraglutide ($iAUC_{0-4h}$: -0.87 mmol/L vs. -0.78 mmol/L, IDeg -0.16 mmol/L). Body weight was reduced by 0.5 kg in the IDegLira group as compared to an increase by 1.6 kg in the IDeg group and a decrease by 3.0 kg in the liraglutide group.

In study **3912**, where the IDeg dose in both arms was maximised to 50 units, HbA1c decreased by 1.90 % with IDegLira and by 0.89 % with IDeg. The reduction in HbA1c was statistically significantly greater with IDegLira compared with IDeg. The HbA1c targets of 7% and 6.5% were reached by 60.3% and 45.2% of IDegLira-treated subjects as compared to 23.1% and 13.1% of IDeg-treated subjects. No difference in insulin dose was observed between treatment arms with a mean insulin dose of 45 units for both arms at week 26.

The primary endpoint was supported by significant reductions in FPG with IDegLira compared to IDeg (-3.46 mmol/L vs. -2.58 mmol/L). The SMPG profile which includes both the effect on FPG and post-prandial glucose increment was also lower with IDegLira compared to IDeg. After 26 weeks of treatment, a change in body weight from of -2.7 kg and 0.0 kg was observed for IDegLira and IDeg, respectively.

Transferring patients on basal insulin applying a starting dose of 16 dose steps IDegLira appears feasible and did not result in loss in metabolic control during the transition period.

Uncertainty in the knowledge about the beneficial effects

In study 3948, the active comparator IAsp was used once daily with the main meal. Participant in this trial were subjects not sufficiently controlled on insulin + metformin in spite of participation in clinical trials during 2 years. These patients were in need for intensification of treatment, and it is unlikely that IAsp administered once daily will be sufficient. Multiple daily injections will be needed in these

subjects.

In the studies, the combinations IDeg+liraglutide+metformin or IDegLira+metformin+/-pioglitazone or IDegLira + metformin or IDet+liraglutide+metformin have been studied and there is consequently no data on liraglutide and basal insulin added to SU therapy or insulin glargine in combination with liraglutide or the combination basal insulin + liraglutide without metformin. Studies, with these specific combinations are ongoing.

The currently proposed indication states that Victoza should be used "in combination with oral glucose-lowering medicinal products and/or basal insulin". Concomitant use with SU and basal insulin has not been studied.

Risks

Unfavourable effects

The most common adverse events associated with liraglutide in combination with insulin are gastrointestinal side effects, comparable to liraglutide use. In study **3948** the incidence for IDeg +Liraglutide, IDeg + IAsp, respectively were; nausea (20.7 and 1.2 %), diarrhoea (10.3 and 1.2%), vomiting (5.7 and 0%). In study in study **3697** the incidence for IDegLira, IDeg and Lira, respectively were; nausea (10.3, 3.9, 22.3 %), diarrhoea (10.2, 6.8, 16.3%), vomiting (5.0, 2.4, 9.2%). The GI AEs were transient.

In study **3948**, the observed rate of confirmed hypoglycaemia was 100 and 815 episodes per 100 PYE with IDeg + liraglutide and IDeg + IAsp, respectively with an 87% lower estimated rate with IDeg + liraglutide; estimated rate ratio: 0.13 [0.08; 0.21]95%CI. The observed rates of nocturnal hypoglycaemia were 17 and 111 episodes per 100 PYE with IDeg + liraglutide and IDeg + IAsp, respectively; estimated rate ratio 0.14[0.05; 0.40]95%CI.

In study **3697**, the percentage of subjects who experienced confirmed hypoglycaemic episodes during the first 26-week treatment period was 31.9% in the IDegLira group compared to 38.6% in the IDeg group and 6.8% for liraglutide. In Trial **3912**, the proportions of subjects experiencing confirmed hypoglycaemic episodes were 24.1% and 24.6% for IDegLira and IDeg, respectively (rate; IDegLira 153.4 events, IDeg 263.3 events per 100 PYE).

The incidence of allergic reactions seen in the IDegLira treated group in the pooled safety analysis set (3697 and 3912) was 0.9%. Injection site reactions related to IDegLira treatment was present in 2.9% of patients compared to 4.6% for Lira and 2.9% for IDeg.

Five (5)% of patients treated with IDegLira had an increase in antibodies to human insulin or specific insulin antibodies to insulin compared to 2% of patients treated with IDeg in study 3697. In study 3912, the percentages were 5 and 3% for I IDegLira and IDeg, respectively. No neutralising insulin anti-bodies were detected. Few subjects developed anti-liraglutide antibodies (0.5-3% at different time points in the IDegLira group). Antibodies were not tested in study 3948.

No confirmed episodes of pancreatitis were reported in the liraglutide and basal insulin groups. However, a mean increase of serum lipase and amylase was seen the IDeg and liraglutide and liraglutide groups compared to patients treated with IDeg. Acute pancreatitis has been previously identified as a potential safety issues for the GLP-1 receptor agonist class. Pancreatitis should be included in the RMP as important identified risk.

Uncertainty in the knowledge about the unfavourable effects

The rate of neoplasm events in trial 3948 was 3 in the IDeg+liraglutide group and 2 in the IDeg+Iasp group. In the pooled data of 3697 and 3912 in the IDegLira group 3.3 events per 100 PYE were reported, for IDeg 2.5 events and for Lira 3.3 events per 100 PYE groups. The event rate with IDegLira was mainly driven by skin events (4 events of 'basal cell carcinoma' and 1 event of 'malignant melanoma'). No medullary thyroid cancer event was reported in any of the treatment groups. As a result of the recent art 5(3) procedure, pancreatic cancer should be included in the RMP as a potential risk.

The safety data base is too small to draw conclusions with respect to cardiovascular safety. However, as also remarked in the Assessment Report for IDegLira, it is unclear why only 40 of the 216 cardiovascular events identified by search qualified for adjudication and were sent to the EAC.

There is no indication of an additive effect with respect to the risk of hypoglycaemia when IDeg is combined with Lira. However, there were 3 hypoglycaemia SAEs reported in patients on IDegLira which should be further discussed especially with respect to possible medication errors. The rates of confirmed hypoglycaemia were slightly higher in the elderly in the pivotal study in both study groups in the pivotal study.

There is limited experience of use of liraglutide and basal insulin in patients with congestive heart failure NYHA class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV.

The incidences of AEs were similar in patients below and above age 65 years, but the number of subjects ≥ 75 years is very low.

The clinical experience of liraglutide and basal insulin in patients with moderate renal impairment is very limited (n=11) and use should not be recommended in line with recommendations for Victoza.

There is no clinical experience of liraglutide and basal insulin administered alone or in combinations with other oral antidiabetic drugs than metformin or a combination of metformin and pioglitazone (n=140).

There is no clinical experience of liraglutide in combination with insulin glargine.

Benefit-risk balance

Importance of favourable and unfavourable effects

The pivotal study 3948 and trial 3912 show that the addition of liraglutide to basal insulin in subjects failing on insulin+OADs results in a clinically relevant effect in terms of HbA1c lowering. In study 3948, the incidence of hypoglycaemia was lower with IDeg+Lira compared to IDeg+IAsp, in spite of the fact that the dose of IAsp apparently was too low for an effect on HbA1c. In study 3912 no difference in rate of hypoglycaemia was seen; however the effect on HbA1c was larger in the IDegLira group compared to IDeg. In this trial the dose of IDeg was limited to 50 units.

In study 3697 also clinically relevant effects on HbA1c were found with IDegLira. However, subjects in this trial were insulin naïve, and thus not quite comparable to the target population for the claimed indication.

The effect on body weight was not entirely consistent across the studies, but the combination is at least weight neutral, compared to weight increase with IAsp or IDeg, which is important in the T2DM population where overweight is often a problem.

The safety profile for basal insulin and liraglutide is in general similar to the two included mono-components with no indications of additive toxicity. When using IDegLira, GI adverse events were lower compared to liraglutide given as monotherapy. This is due to the titration scheme for IDegLira and results might be misleading for liraglutide as add-on therapy, where titration steps are larger.

No confirmed episodes of pancreatitis were reported with the combined use of basal insulin and liraglutide, but have been reported for other GLP 1 agonists. Acute pancreatitis has previously been identified as a potential safety issues for the GLP-1 receptor agonist class and the risk, albeit small, should be taken into account when prescribing these products.

Other issues discussed for the GLP 1 agonists include risk of thyroid and pancreatic neoplasm. The current data base is too limited and the duration of the studies too short to provide any useful information. Long term PAS studies are ongoing for both Lira and IDeg which will provide more information, but there are currently no indications of an increased risk. As a result of the recent art 5(3) procedure, pancreatic cancer should be included in the RMP as a potential risk.

Currently, data on CV outcomes are still limited. Several CV outcome studies are ongoing, no further action is needed at the moment.

In conclusion, for patients eligible for intensification of insulin treatment, Victoza may be a valuable alternative to adding only insulin/increasing the insulin dose since Victoza was shown to provide a superior HbA1c reduction combined with weight stability and a lower incidence of hypoglycaemia. However, Victoza and basal insulin are not investigated without metformin to date and furthermore, this combination is not tested with the combined use with SU.

Benefit-risk balance

The benefit-risk balance is currently positive.

Discussion on the benefit-risk balance

The combination of basal insulin and a GLP-1 analogue in the treatment of T2DM has been previously evaluated and accepted for other products.

The combined use of two drugs in case one of the drugs has shown insufficient results with complementary mechanisms of action by a) substituting for the relative insulin deficiency in T2DM and b) stimulate the endogenous insulin secretion is an adequate rationale and carries the potential of sparing beta-cell function over time.

The appropriate target population for liraglutide as add-on to basal insulin could primarily be patients eligible for intensification of insulin treatment. This would include patients not adequately controlled on metformin and insulin (study 3948), not adequately controlled on metformin, insulin and SU (study 3912). Liraglutide provided a superior glycaemic control compared to adding IAsp with the largest meal combined with the benefit of weight stability. An alternative treatment strategy could have been to increase the insulin dose further, but this would very likely have been associated with increased risk of hypoglycaemia and weight increase.

Trial 3697 did not include the target population for the claimed indication, and trial 1842 did not investigate the effect of liraglutide.

Concerning safety data for IDeg and liraglutide separately, this has been extensively assessed in the context of marketing approval applications for Tresiba and Victoza. Further, recently an article 5(3) procedure has been finalized reviewing pancreatic safety associated with the use of GLP 1 agonists.

The extent of the exposure to the combination Victoza with insulin in the current application is considered as sufficient to assess short term safety.

In the submitted studies, all subjects received study treatment as add-on to metformin +/-pioglitazone and liraglutide with basal insulin has not been evaluated in combination with other OADs (study in combination with SU is ongoing), or in patients with insulin glargine treatment (study ongoing), or in patients with basal/bolus insulin regimen. Concomitant use of liraglutide with SU and basal insulin has not been studied. The new, broad indication might suggest that Liraglutide can be combined with insulin plus all OADs. This is inherent to the indication, which was approved for all SGLT-2 inhibitors. In section 5.1 all combinations that are studied are mentioned. For SGLT-2 inhibitors this was considered sufficient, so it can be accepted for Victoza too.

GLP-1 receptor agonists have been associated with thyroid C-cells proliferative/hyperplasia in non-clinical carcinogenicity studies, but the relevance for humans is unsure. The potential tumor growth promoting effect of insulin analogues due to their anabolic properties is an ongoing discussion. However, no firm association has been established between any insulin analogues and increased cancer risk. An additive effect on the risk of malignancies when combining Lira and IDeg could be hypothesized. However, this risk seems very remote and is not considered strong enough to justify a request for specific PAS studies. Long term post-authorisation safety studies are ongoing for both Lira and IDeg which will provide more information about neoplasms.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.4, 4.7, 4.8 and 5.1 of the SmPC in order to include information on the use of liraglutide in combination with basal insulin. The Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.