PASS Information

Title	Utilisation of dulaglutide in European countries: A cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases
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Date of last version of the final study report	N/A
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Product reference:	EU/1/14/956
Procedure number:	EMEA/H/C/002825
Marketing authorisation holder(s)	Eli Lilly Nederland B.V.
Joint PASS	No
Research question and objectives	The purpose of this study is to describe how dulaglutide is used among different patient groups in Europe. Primary objective: To describe the frequency of dulaglutide use in the population and characterise by age, gender, main comorbidities, and main co-prescriptions overall and in the following subgroups of interest: o Populations of interest: • Patients with severe renal failure • Patients with hepatic disease • Patients with heart failure • Patients with severe gastrointestinal disease • Children and adolescents (<18 years of age) • Elderly patients (≥75 years of age) • Pregnant or breast-feeding women o Medication use: • Medication errors • Off-label use Secondary objective: To describe the off-label use among each of the above populations of interest.
Country(-ies) of study	France, Germany, Spain, Sweden and the United Kingdom
Author	PPD
Signature of principal investigator	Signature on file/see approval date below

Approval Date: 14-Nov-2019 GMT

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V. Papendorpseweg 83, 3528 BJ Utrecht The Netherlands
MAH contact person	PPD Eli Lilly and Company

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1. Abstract

Title

Utilisation of dulaglutide in European countries: A cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases

Keywords

Drug utilisation study, dulaglutide, treatment characteristics

Rationale and background

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin mimetics that are widely used as glucose-lowering drugs in the treatment of patients with type 2 diabetes mellitus (T2DM). Dulaglutide is a long-acting GLP-1 RA that was approved in the European Union (EU) for the treatment of T2DM in November 2014. This drug utilisation study (DUS) aimed to describe the use of dulaglutide overall and in subpopulations of patients for whom little data existed at the time of initial authorisation, as well as off-label use and medication errors, i.e., prescribing dulaglutide in >1 weekly dose.

Research question and objectives

To describe the frequency of dulaglutide use among populations of interest for which little data was available in initial registration clinical trials, including patients with severe renal failure, hepatic disease, heart failure, and severe gastrointestinal (GI) disease; children and adolescents; elderly patients (≥75 years old); and pregnant and breast-feeding women in Europe. In addition, to describe medication errors (defined as prescribing dulaglutide to patients with T2DM in >1 weekly dose) and off-label use (defined as prescribing dulaglutide to patients without diagnosis of T2DM, or prescribing dulaglutide as first-line therapy to patients with T2DM) overall and among populations of interest.

Study design

Multi-country, multi-source, cross-sectional, descriptive study using longitudinal data collected from European electronic health record (EHR) databases.

Setting

The study was conducted in the outpatient setting in five Europe selected from the EHR databases: France, Germany, Spain, Sweden, and the United Kingdom (UK).

This final study report presents data retrieved from France, Germany, Spain, Sweden, and the UK, on patients who initiated dulaglutide at any time between January 1, 2015 and December 31, 2017.

Subjects and study size, including dropouts

Study population included all patients for whom a treatment with dulaglutide was initiated during the observation period for whom at least 6 months of continuous medical history was available prior to the date of first dulaglutide prescription.

Variables and data sources

Patient demographics, disease characteristics, and prescription details were extracted and analysed at baseline (6-month period prior to dulaglutide initiation) and/or index date (dulaglutide initiation) using the following European EHR databases:

- France: IQVIA Disease Analyzer
- Germany: IQVIA Disease Analyzer
- Spain: The Information System for the Development of Research in Primary Care
- Sweden: National Patient Register and Swedish Prescribed Drug Register
- UK: Clinical Practice Research Datalink

Results

Between 1 January 2015 and 31 December 2017, a total of 15,619 dulaglutide initiators were eligible for analyses, corresponding to 5,456 in Sweden, 4,759 in Germany; 2,716 in Spain; 1,384 in France; and 1,304 in the UK. All dulaglutide initiators in Germany and the UK, and the vast majority of patients in Sweden, Spain, and France were diagnosed with T2DM. More than 50% of dulaglutide initiators across the five Europe were between the ages of 45 and 64 years.

The populations of interest are not mutually exclusive, whereby a patient could be part of more than one group, e.g. a dulaglutide initiator with a history of heart failure could be an elderly patient. Overall, no children or adolescents were identified among initiators of dulaglutide with the exception of PPD
Overall, slightly more than one-third of dulaglutide initiators were elderly patients (≥65 years of age); those aged ≥75 years comprised from 7 to 10% of dulaglutide initiators in all countries, except in the UK (4.7%). Among women treated with dulaglutide, PPD

Less than 1.5% of patients had pre-existing severe renal failure across the five countries (France: none, Germany: 0.5%, Spain: 1.3%, Sweden: 0.5%, and the UK: 0.3%). The frequency of hepatic disease among patients treated with dulaglutide was 0.7% in France, 3.2% in Germany, 16.6% in Spain, 1.9% in Sweden, and 7.7% in the UK. Patients with heart failure accounted for 1.5% of dulaglutide initiators in France, 10.6% in Germany, 6.6% in Spain, 7.2% in Sweden, and 3.2% in the UK. Patients with severe GI disease were 4.9% in France, 8.1% in Germany, 10.6% in Spain, 8.6% in Sweden, and 17.9% in the UK.

The present data show that between 95% and 100% of dulaglutide initiators were diagnosed with T2DM at the time of treatment initiation, with the vast majority being previously treated with other anti-diabetes medications, including at the time of treatment with dulaglutide. This could

reflect prescribing dulaglutide according to the label for T2DM, and as an add-on therapy rather than first-line T2DM therapy. The mean duration of diabetes varied among first-time users of dulaglutide, with relatively shorter duration observed in Germany and France (4-5 years), compared to a longer duration in Spain, Sweden and the UK (8-10 years). The duration of diabetes treatment appeared to be consistent with the duration of underlying diabetes. The average weekly dose of dulaglutide among initiators was relatively similar across study countries.

Up to 5% of dulaglutide initiators were prescribed dulaglutide in >1 weekly dose , with the exception of the UK where it was reported for 84.3% of patients. This high reported value can be attributed to administrative overlaps in the source data.

Pre-existing hypertension was present in 60% to 85% of patients who started treatment with dulaglutide. Dyslipidaemia was also prevalent in 60% to 82% of patients with the exception of the UK where it was reported to be prevalent in 26.8% of patients. Macrovascular complications were reported in 67% to 87% of patients in France, Germany, Sweden, and the UK while Spain reported 18.7% with macrovascular complications. Microvascular complications were observed to be less than 50% overall. The distribution of these complications, however varied across countries. Overall, between 1-3% of dulaglutide initiators had histories for solid tumours, with 0.5 to 1.4% affecting the breast.

The majority of dulaglutide initiators across all countries were reported to have prior use of other ADMs during the 6-month baseline study observation period (78% to 97%). Among previous ADMs, biguanides, accounted for most of the prior medication use in France (53%), Sweden (75%) and the UK (63%) whereas insulins accounted for most of the ADM use in Germany (53%) and Spain (35%). Biguanide use at index date accounted for the majority of concurrent ADMs in France (76%), Sweden (61%) the UK (53%), and Spain (40%); however, most of the patients in Germany (28%) were prescribed insulins.

Clinical laboratory tests for dulaglutide initiators were documented in all countries except Sweden. Among countries with available laboratory test results, a majority of patients were reported to have HbA1c > 7.5% and eGFR ≥ 30 mL/min/1.73 m^2. A majority of the patients had serum creatinine < 100 µmol/L with Spain having the highest proportion of patients, followed by Germany and the UK. Urine albumin/creatinine ratio (UACR) was documented in patients from Spain and the UK with most patients having UACR < 30 mg/g (UK: 91.7% and Spain: 62.4%). Among patients with reported laboratory test results, a majority across all countries had LDL cholesterol < 1.6 g/L, with Spain accounting for 89% of their population, whereas HDL cholesterol value was ≥0.35 g/L with France accounting for 81.9%. The mean LDL and HDL cholesterol was highest in patients from Spain (2.6 g/L and 0.9 g/L, respectively). Across all countries, a majority of the patients had AST and ALT values of < 2*ULNR among both female and male patients (> 91%), with the exception of the UK, where 73.3% of female patients had AST < 2*ULNR. Among both females and males, the mean AST and mean ALT levels were highest in Germany (AST - females: 37.4 IU/L and males: 41.3 IU/L; ALT - females: 47.4 IU/L and males: 56.9 IU/L).

Between 56% and 100% of dulaglutide initiators were prescribed concomitant medications. The distribution of types of concomitant medications varied across the five countries. Lipid modifying agents were frequently prescribed in patients from France (98.9%), the UK (72.2%), and Sweden (69.9%); whereas, vasodilators acting on the renin-angiotensin system were commonly prescribed across all countries except Spain, where a high proportion of patients were prescribed analgesics (69.4%), followed by systemic antibacterials (65.2%), and anti-inflammatory and anti-rheumatic drugs (56.3%).

Discussion

This final report provides insights on the utilisation of dulaglutide among populations of interest in five European countries. Results indicate that dulaglutide initiators included a low proportion of patients with severe renal failure, hepatic disease, heart failure, severe gastrointestinal disease, children and adolescents, elderly patients, or pregnant or breast-feeding women. Dulaglutide is generally being prescribed to the intended population according to the labelled indication in France, Germany, Spain, Sweden, and the UK. The results and conclusions are consistent with the interim study reports.

Marketing Authorisation Holder(s)

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

Names and affiliations of principal investigators

PPD

Email: PPD

2. List of abbreviations

Term	Definition
ADM	Anti-diabetes medication
ALT	Alanine amino transferase
AST	Aspartate amino transferase
ATC	Anatomical Therapeutic Chemical
AWD	Average weekly dosage
BMI	Body mass index
CPRD	Clinical Practice Research Datalink
DA	Disease Analyzer
DPP-4	Dipeptidyl peptidase-4
DUS	Drug utilisation study
eCAP	Primary Care e-records
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
EMA	European Medicines Agency
EphMRA/ATC	European Pharmaceutical Market Research Association/Anatomical Therapeutic Chemical
ERB	Ethical Review Board
EU	European Union
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GP	General practitioner
GVP	Good Pharmacovigilance Practices
HbA1c	Haemoglobin A1c (glycosylated haemoglobin)
HDL	High density lipoprotein
ICD-10	International Classification of Disease, 10th version
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISPE	International Society for Pharmacoepidemiology
LDL	Low density lipoprotein
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service

Term	Definition
NIHR	National Institute for Health Research
NPR	National Patient Register
PRAC	Pharmacovigilance Risk Assessment Committee
Q1	First quartile
Q3	Third quartile
RA	Receptor agonist
RMP	Risk management plan
RWES	Real-World Evidence Solutions
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SIAP	Catalan Health Service Database
SIDIAP	The Information System for the Development of Research in Primary Care
SOP	Standard operation procedure
SPDR	Swedish Prescribed Drug Register
T2DM	Type 2 diabetes mellitus
UACR	Urine Albumin-to-Creatinine Ratio
UK	United Kingdom

3. Investigators

Principal Investigator:

PPD

Email: PPD

Project Team:

Coordinating investigator:
PPD

Coordinating investigator in Sweden:
PPD

Coordinating investigator in France:
PPD

Coordinating investigator in Germany:
PPD

4. Other responsible parties

Project team:

Sponsor: Eli Lilly and Company

Sponsor's EU Qualified Person for Pharmacovigilance (QPPV):

PPD
Eli Lilly and Company
Surrey, UK GU20 6PH
Email: PPD

Main Author: IQVIA, RWES/HEOR Department

PPD
Email:PPD

Co-Author: IQVIA, RWES/HEOR Department

PPD
Email: PPD

Co-Author: Eli Lilly and Company

PPD
Eli Lilly Corporate Center
Indianapolis, IN 46285, USA
Email: PPD

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	Estimated Quarter 3 2016	01 May 2017	
End of data collection	Estimated Quarter 2 2019	12 June 2017	
Registration in the EU PAS register	Estimated Quarter 1 2016	14 June 2016	
Feasibility assessment report	Estimated Quarter 3 2016	26 May 2017	
Interim report 1	Estimated Quarter 4 2016	NA	Feasibility study results showed that uptake in France, Spain, and the UK was limited in 2015
Interim report 2	Estimated Quarter 4 2017	15 November 2017	Includes analyses and results for interim report 1 and interim report 2
Interim report 3	Estimated Quarter 4 2018	23 October 2018	Includes analyses and results for January 2017 to December 2017
Final report of study results	Estimated Quarter 4 2019 (i.e. approximately 5 years from market authorisation)	See Page 1	

6. Rationale and background

Glucagon-like peptide-1 (GLP-1) is a naturally occurring peptide incretin hormone released from the gut into circulation upon meal intake and enhances glucose-dependent insulin secretion. GLP-1 has multiple physiological effects that make it an attractive therapeutic target for type 2 diabetes mellitus (T2DM). GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4), resulting in a short plasma half-life (1.5-5 min) and would require continuous administration. In patients with T2DM, there is an impaired function of GLP-1 which has led to the development of GLP-1 receptor agonists (RAs) with a longer half-life and beneficial glycemic effects [1, 2]. GLP-1 RAs are incretin mimetics which are widely used as glucose-lowering drugs in the treatment of T2DM [3] and are not broken down by DPP-4s. Similar to endogenous hormone GLP-1 [4], they inhibit glucagon secretion, delay gastric emptying, and suppress appetite. They stimulate insulin secretion in a glucose-dependent manner; insulin release stops when the plasma glucose level is low (3 mmol/l) [5].

Over the years, GLP-1 RAs have become integral in T2DM treatment [6]. Six GLP-1 RAs are currently approved worldwide for treatment of adults with T2DM: exenatide (2 forms with daily/weekly administration: Byetta® was approved by the European Medicines Agency (EMA) in November 2006/Bydureon® in 2011, AstraZeneca), liraglutide in July 2009 (Victoza®, Novo Nordisk), lixisenatide in February 2013 (Lyxumia®, Sanofi), albiglutide in March 2014 (Eperzan®, GlaxoSmithKline), dulaglutide in November 2014 (Trulicity®, Eli Lilly and Company), and semaglutide in December 2017 (Ozempic®, Novo Nordisk). Additionally, one formulation which comprises insulin degludec and liraglutide (Xultophy®, Novo Nordisk), as single device combination therapy was approved in September 2014.

Dulaglutide is a long-acting GLP-1 RA. Its structure protects it from degradation by DPP-4 and confers a half-life up to approximately 5 days in humans [7]. The long half-life results in once weekly administration of dulaglutide, which may offer an advantage compared to some competitors such as short-acting exenatide, which is given twice daily, and liraglutide or lixisenatide, which are used once daily. Notably, long-lasting exenatide (Bydureon®), albiglutide (Eperzan®), and semaglutide (Ozempic®) are also used once weekly. The European Union (EU) Commission approved dulaglutide solution for injection for the treatment of T2DM in November 2014 and became available in EU countries beginning January 2015 [8].

As part of the risk management plan (RMP), Eli Lilly, the Marketing Authorisation Holder (MAH) of dulaglutide, conducted a drug utilisation study (DUS) to describe the use of dulaglutide in subgroups of patients across several databases in Europe, and to gain knowledge about off-label use (defined as prescribing dulaglutide to patients without a diagnosis of T2DM, or prescribing dulaglutide as first-line therapy to patients with T2DM), medication errors (defined as prescribing dulaglutide to patients with T2DM in >1 weekly dose), and the use in subpopulations of patients for which little data existed at the time of initial registration (i.e. patients with severe renal failure, heart failure, hepatic disease, or severe gastrointestinal disease; children and adolescents with T2DM (<18 years of age); elderly patients (≥75 years); and pregnant or breast-feeding women).

7. Research question and objectives

The purpose of this study was to describe the prescribing patterns of dulaglutide among different patient groups in Europe.

The ***primary objective*** was to describe the demographics and clinical characteristics among patients initiating dulaglutide overall and within the following subgroups of interest:

- Populations of interest:
  - Patients with severe renal failure
  - Patients with hepatic disease
  - Patients with heart failure
  - Patients with severe gastrointestinal disease
  - Children and adolescents (<18 years of age)
  - Elderly patients (≥75 years of age)
  - Pregnant or breast-feeding women

- Medication use:
  - Medication errors (prescribing dulaglutide to patients with T2DM in >1 weekly dose)
  - Off-label use (prescribing dulaglutide to patients without diagnosis of T2DM, or prescribing dulaglutide as first-line therapy to patients with T2DM)

The ***secondary objective*** was to describe the off-label use among each subgroup population of interest.

8. Amendments and updates

None.

9. Research methods

9.1. Study design

This was a multi-country, multi-source, cross-sectional, descriptive study using longitudinal data collected from European electronic health record (EHR) databases. These data sources include information on written or dispensed prescriptions, patient's demographics, and diagnoses.

Five countries were selected from the databases under consideration (France, Germany, Spain, Sweden, and the United Kingdom [UK]). The justification of the selected countries was based on the feasibility assessment results and the market uptake and volume of dulaglutide in each country.

Study Period

The study was planned to be conducted for at least three years post launch of dulaglutide (i.e. until January 2018). The analyses and reporting were initiated approximately one year after the launch of dulaglutide, as soon as the data on 1,000 initiations of dulaglutide were available in the databases with at least 100 patients available in the smallest contributing country.

Three waves of data extraction/collection and analysis were planned to be performed within at least three years, based on launch projections:

- 1st wave: Q3 2016 (covering patients having initiated the drug from Q1 to Q4 2015)
- 2nd wave: Q2 2017 (covering patients having initiated the drug from Q1 to Q4 2016)
- 3rd wave: Q2 2018 (covering patients having initiated the drug from Q1 to Q4 2017)
- 4th wave: Q2 2019 (final report covering patients' data from the previous three waves from Q1 2015 to Q4 2017)

Results from a feasibility study showed that uptake in France, Spain, and the UK was limited in 2015. Although the number of patients in 2016 was sufficient for the five targeted countries, local administrative issues did not allow data extraction from the UK within the time period needed to complete analyses for the first interim report. Therefore, the first interim report provided findings for four of the targeted countries: France, Germany, Spain, and Sweden. Data from the 1st and 2nd waves of data collection were combined into a single dataset for each country and presented in the first interim report.

Results for the second interim report included data from the 3rd wave of data collection for France Germany and Spain. However, local administrative issues did not allow data extraction from Sweden and the UK within the time period needed to complete analyses for the 3rd wave of data collection. Therefore, the second interim report provided findings for three of the targeted countries: France, Germany, and Spain.

This final study report includes data from the previous three waves of analyses from 2015 to 2017 for all five targeted countries: France, Germany, Spain, Sweden, and the UK.

9.2. Setting

This study was conducted using electronic longitudinal databases including data collected in outpatient settings of the target countries.

The choice of countries was based on the following criteria:

- Selected countries should have a high number of patients exposed to dulaglutide
- Selected countries should have available longitudinal databases with available information required to meet the study objectives

9.3. Subjects

The study population included all patients receiving dulaglutide prescriptions in the outpatient setting in the selected databases of five European target countries (i.e. France, Germany, Spain, Sweden, and the UK). The eligible patients were those for whom treatment with dulaglutide was initiated during the observation period in each wave of the study for patients having at least 6 months of available continuous history prior to the date of the first dulaglutide prescription (i.e. baseline period). There were no exclusion criteria applied in this study.

The use of dulaglutide was analysed overall and within the following subgroups of patients:

- Populations of interest:
  - Patients with severe renal failure
  - Patients with heart failure
  - Patients with hepatic disease
  - Patients with severe gastrointestinal disease
  - Children and adolescents (<18 years of age)
  - Elderly patients (≥75 years of age)
  - Pregnant or breast-feeding women
- Medication use:
  - Medication errors (prescribing dulaglutide to patients with T2DM in >1 weekly dose)
  - Off-label use (prescribing dulaglutide to patients without diagnosis of T2DM, or prescribing dulaglutide as first-line therapy to patients with T2DM)

9.4. Variables

Different populations and subgroups of interest were defined as follows, regardless of the coding system used in EHR databases:

1. Treatment initiation with dulaglutide:
   - any record of prescription of dulaglutide during the observation period without prior record of prescription of the same product in the available patient's history
   - if no prior history is available to check the above criteria, the prescription is not considered as an initiation

2. Patients presenting with T2DM:
   - with any recorded diagnosis code for T2DM
   - or with any recorded treatment code for an anti-diabetes medication (ADM) other than insulin
   - or, with any recorded treatment code for insulin initiated at age >30 (defined as no record of insulin therapy during 6 months prior to first record of insulin treatment)
   - or with any record of unspecified diabetes mellitus diagnosis at age >30 and without a history of insulin therapy (defined as no record of insulin therapy during 6 months prior to the first record of diabetes diagnosis)

3. Patients with severe renal failure:
   - with a recorded diagnosis of severe renal failure
   - or with a recorded estimated glomerular filtration rate (eGFR) value <30 ml/min/1.73 m^2

4. Patients with hepatic disease:
   - with a recorded diagnosis of any hepatic disorder

5. Patients with heart failure:
   - with a recorded diagnosis of heart failure

6. Patients with severe gastrointestinal disease:
   - with a recorded diagnosis of any of the following conditions:
     - cancer of the gastrointestinal tract,
     - diseases of the oesophagus,
     - active ulcer at the time of drug initiation (gastric, duodenal, gastro-jejunal, peptic ulcer, of unspecified site),
     - active haemorrhagic gastritis, chronic atrophic gastritis, adult hypertrophic pyloric,
     - stenosis, obstruction of duodenum, and other motility disorders,
     - digestive fistula,
     - Crohn's disease, ulcerative colitis,
     - diverticular disease of the intestine,
     - severe vomiting, severe diarrhoea, and severe constipation,
     - motility disorders, including ileus, gastroparesis, et cetera,
     - infectious and inflammatory situations (appendicitis, cholecystitis, cholangitis)

7. Children and adolescents:
   - Age < 18 at the time of treatment initiation (subgroups of analysis: 0-4, 5-9, 10-14, and 15-17 years old)

8. Elderly patients:
   - Age ≥75 at the time of treatment initiation

9. Pregnant and breast-feeding women:
   - Any record of pregnancy or breast-feeding at the time of treatment initiation

10. Patients with medication errors:
    - Prescribed > 1 dose per week of dulaglutide [9]
        - Note: The number of doses/week was calculated by measuring the time span between the current prescription and the next one (in weeks) and dividing the number of injections prescribed in the current prescription by this time span. This number of doses/week was used in the cross-sectional study as an attribute of the prescription to assess the occurrence of medication errors as described above

11. Patients with off-label use:
    - Prescribed dulaglutide with no diagnosis of T2DM as defined above.
    - Prescribed dulaglutide with a diagnosis of T2DM as defined above and without a record of other ADMs during the 6-month baseline period, i.e. dulaglutide was prescribed as first-line therapy

9.4.1. Measurements of interest

The following variables were analysed in each subgroup of interest and among patients initiated with dulaglutide:

- Patients' demographics (i.e. age and gender) and clinical parameters (i.e. height, weight, body mass index [BMI]) at baseline
- Relevant comorbidities
- Medical history: disease diagnoses (using appropriate disease classification)
- Concomitant ADMs
    - Any medication that might be prescribed to the patient at the same time as dulaglutide was considered a concomitant medication. Because medications might be prescribed chronically, the look-back window for assessing concomitant medications was 90 days (i.e. 3 months). Therefore, any medication prescribed during the 3 months prior to index date was considered as concomitant medication to dulaglutide
- Other drug exposures (main therapeutic classes)
- Average weekly dosage of dulaglutide prescriptions
- Prescriptions in combination with other ADMs

9.4.2. Collected variables

To assess the above subgroups and measurements of interest, several variables were extracted from each database whenever available: demographics, medical history, treatment, clinical, and clinical laboratory data on patients. These variables along with their corresponding International Classification of Disease, 10th version (ICD-10) codes are shown in Table 9.3.2-1 of the study protocol (Version 1.0, June 2016).

9.5. Data sources

The European EHR databases were used to evaluate dulaglutide uptake, volume, and data availability. Based on potential expected sales volume of dulaglutide and uptake in the countries as well as the availability of data, the following European EHR databases were pre-selected for this study:

- France: IQVIA Disease Analyzer (DA) (French-DA)
- Germany: IQVIA Disease Analyzer (German-DA)
- Spain: The Information System for the Development of Research in Primary Care (SIDIAP)
- Sweden: the National Patient Register (NPR) and the Swedish Prescribed Drug Register (SPDR)
- UK: Clinical Practice Research Datalink (CPRD)

9.5.1. Disease analyser in France and Germany

The IQVIA Disease Analyzer (DA) is a longitudinal patient database providing information from continuing physician and patient interactions on consultations, diagnoses, and treatments. This database is available in France and Germany. Anonymous data are collected continuously through the medical software, allowing longitudinal follow-up of all the different visits of the same patient consulting the same general practitioner (GP) in the panel. The collected data include administrative (for example, insurance scheme, socioeconomic status), demographic (for example, age, gender, region), anthropometric (for example, height, weight, BMI), clinical (signs, symptoms and diagnoses according to ICD-10 classification), laboratory (laboratory test results reported by the physicians) and therapeutic (European Pharmaceutical Market Research Association/Anatomical Therapeutic Chemical [EphMRA/ATC] class, molecule / brand name, dosage, route of administration) information. An update of the database is done monthly with a lag time of 6 weeks.

Comparisons with external data sources (for example, data from statutory health insurances) underline the validity and representativeness of the German-DA in pharmacoepidemiological and pharmacoeconomic studies [10].

The DA is currently used by the EMA as one of its resources for answering research questions.

<u>DA in France:</u>

The data collection is based on five different EHR applications used by 1,200 GPs. The French database is representative in terms of GP distribution, patient profile, age group, and sex. It allows for a longitudinal follow-up of all the different visits of the same patient consulting the same GP in the panel. Due to the role of GPs as the first point of care in France, the loyalty of patients to GPs is very high and each GP provides a continuous follow-up of patients.

DA in Germany:

The German-DA is based on patient records continuously collected from 2,400 computerised practices (including 1,400 GPs and 1,000 specialists), using three different EHR applications. The sample is designed to be representative of Germany (10).

9.5.2. SIDIAP in Spain

The SIDIAP database contains information from 274 primary care centres in Catalonia, Spain, with a source population of 5.5 million patients which encompasses 80% of the total Catalan population. The SIDIAP aims to register all health information with research value in an anonymised database for every patient.

The Primary Care e-records (eCAP) database which contains information on primary care since 2000 is the basis of the source population in SIDIAP. Various external data sources can be linked to eCAP as required to provide a more complete picture of the cohort profile. In this study, it is proposed to use eCAP, Catalan Health Service Database (SIAP), Pharmacy Official Invoice Database, Primary Care Lab Database, and CMBD-AH to capture the parameters required in this study.

9.5.3. NPR and SPDR in Sweden

The Swedish database combines data from the NPR, covering all specialist and hospital care in Sweden, and the SPDR, covering all drugs dispensed at all community pharmacies in Sweden. The national registers are updated at least quarterly. These longitudinal data enable researchers to assess comorbidities, other clinical characteristics, and filled drug prescriptions in patients initiating dulaglutide in a hospital setting including inpatients, as well as both primary and secondary care. The NPR is known to have generally high validity, with positive predictive values ranging from 85 to 95% for most diagnoses [11]. However, information on patient anthropometric data (height, weight, BMI) are not available through the databases, nor are laboratory test results and clinical measurements such as haemoglobin A1c (HbA1c), blood pressure and blood lipid levels.

Data for Wave 3 for Sweden was not received by a predetermined cut-off date of 16 July 2018 and, therefore, could not be included in the 2018 2nd interim report.

Results for Sweden for Wave 3 are included in this final report submitted to the PRAC. The final report synthesises results from all countries and all data waves into a single report.

9.5.4. CPRD in the UK

The CPRD is a well-validated database with high-quality information on medications, laboratory data, specialist referral and diagnoses assigned by primary care clinicians. It is jointly funded by the National Health Service (NHS) National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA).

The CPRD has one of the world's largest computerised databases of anonymised longitudinal medical records from primary care that is linked with other healthcare data in the UK. Currently,

data are being collected on approximately 5 million active patients from around 683 primary care practices throughout the UK (about 8% of the UK population).

9.5.5. Summary of data sources

All the targeted longitudinal databases provide information on patient's demographics, diagnoses, and drug treatment. The detailed information on parameters availability for country-specific data sources is summarised in Table 9.5.5-1.

Table 9.5.5-1 Data Availability per Database/Country*

Data availability per country (local database)	France (French-DA)	Germany German-DA)	Spain (SIDIAP)	Sweden* (NPR and SPDR)	The UK* (CPRD)
Demographics (i.e. age, gender)	Yes	Yes	Yes	Yes	Yes
Clinical parameters (i.e. height, weight, BMI)	Yes	Yes	Yes	No	Yes
Physiological status: pregnancy breast-feeding women	Very limited	Very limited	Very limited	Very limited	Very limited
Date of consultation	Yes	Yes	Yes	Yes	Yes
Diagnosis	Yes ICD-10 codes	Yes ICD-10 codes	Yes ICD-10 codes	Yes ICD-10 codes	Yes READ codes
Prescribed drug characteristics (name, form, package, classification code)	Yes (EphMRA/ATC codes)	Yes (EphMRA/ATC codes)	Yes (ATC codes)	Yes (ATC codes)	Yes (associated medcodes)
Dosage	Yes	Yes	Yes	Yes	Yes
Duration exposure	Yes	Yes	Yes	Yes	Yes
Co-prescriptions	Yes	Yes	Yes	Yes	Yes
Treatment history	Yes	Yes	Yes	Yes	Yes
Biological test (HbA1c, cholesterol level, creatinine)	Yes	Yes	Yes	No	Yes

*CPRD: Clinical Practice Research Datalink; HbA1c: haemoglobin A1c; ICD-10: International Classification of Disease, 10th version; NPR: National Prescription Registry; SIDIAP: The Information System for the Development of Research in Primary Care; SPDR: Swedish Prescribed Drug Register

9.6. Bias

This section highlights the bias anticipated in the study in terms of selection bias, misclassification bias, and information bias of using anonymised databases within the EHR practice setting. A detailed discussion on the different types of anticipated bias are presented in Section 11.2.

Selection Bias

For all data sources, it must be considered that patients who seek treatment outside the EHR practice setting do not have their records in the database considered for this study.

Also, as a result of no exclusionary criteria in the study design, it can be expected that the selection of the study population did not introduce selection bias.

Misclassification bias

Misclassification bias cannot be controlled as fully anonymised databases were used, therefore it is impossible to verify the information with source data.

Information bias

In EHR databases, information is recorded when clinically useful. Hence, for this study, information bias is likely to be minimal as the data recorded in the EHR for a diabetic patient is that which is clinically relevant for disease management.

9.7. Study size

The real number of eligible patients included in the dulaglutide group depends on the uptake and volume of the drug in each country obtained from respective databases.

According to the calculation of study size with respect to the analysis of the primary objective the required sample size is 384 observations for each country per study period.

$$n = \frac{p \times (1-p) \times z_{1-\alpha/2}{}^2}{e^2}$$

Where the n is the required sample size, p is the proportion of patients/prescriptions with dulaglutide, e is a precision and α is the two-sided first-type error. Considering a confidence interval of 95% and able to determine any percentage with a precision of at least ±5%, the required sample size is 384 subjects.

Feasibility Assessment

Feasibility analyses were conducted to determine when the data sources captured sufficient exposure to dulaglutide, allowing the DUS to start. Each database under consideration was assessed for the following attributes:

- Number of eligible patients (treated with GLP-1 RAs, especially dulaglutide with 6 months of baseline data prior to the first observed/recorded prescription)
- Availability and validity of each variable of interest

The feasibility assessments provided information for the start of data collection. The DUS started as soon as data on 1,000 initiations of dulaglutide were available in the databases, with at least 100 patients available in the smallest contributing country.

9.8. Data transformation

France

Data were stored at the database level. Statistical Analysis System (SAS) Software was utilised for access to the raw data, to manage the analytic datasets and to conduct data analysis. All relevant IQVIA internal SOPs were followed.

Germany

Data selection and retrieval was performed using IQVIA® Disease Analyzer Version 6.6 Build 9. Data were stored at the database level. SAS Software was utilised for access to the raw data, to manage the analytic datasets and to conduct data analysis. This study utilised relevant chapters of ENCePP and ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines for data management.

The IQVIA data was processed according to the standard operating procedures (SOPs) of IQVIA. The datasets extracted from the IQVIA databases were stored in IQVIA files to allow analysis in the future.

Spain

Overall data quality processes are implemented at each phase of the data flow cycle. Quality control checks are performed at the extraction and uploading steps. To assess data completeness the elements presence is described by geographical areas, registering physician, time and the distribution function of values. Correctness is assessed by validity checks on outliers or out-of-range values, formatting errors and logical dates incompatibilities. Completeness and correctness measures are used to inform decisions on the required transformations to improve data quality (harmonisation, normalisation and clean-up) and the data fitness for the purpose of specific research projects.

Specific project data extraction is based on MYSQL script, which generates a SIDIAP data subset including all project variables and specific requested codes. Afterwards, flat tables are built and transferred to the SIDIAP statisticians, who analyses the data using the R (3.4.3 version) and SAS (9.4 version) programs.

Sweden

To access the National Health Registries in Sweden, the local IQVIA project manager submitted an application to the Ethics Review Board (ERB) board in Stockholm, Sweden. Following ERB approval, the local project manager applied for access to data from the National Board of Health and Welfare. Extractions from the following National registers were sought:

- the Patient Register
- the Prescribed and Dispensed Drug Register
- the Causes of Death Register
- the Medical Birth Register

The registers were linked with anonymous patient IDs and only information needed for the described study analyses was obtained. The data were stored as SAS data sets and processed using SAS version 9.4.

United Kingdom

According to data use agreement with CPRD, Eli Lilly provided a data extract from the February 2018 CPRD data release. This contained anonymised patient ID's and only contained information needed for the described study analysis. This data extract was stored on the IQVIA servers following IQVIA SOP's. SAS version 9.4 software was used to access the raw data, provide manipulation required to conduct the analysis and for generating the required summarised results. All relevant IQVIA internal SOP's were followed during this process.

9.9. Statistical methods

The analysis was performed by country. For each country, the analyses were performed on the overall data set of eligible patients and within subgroups.

The different databases resulting from methods of collection with different software, in different countries with different healthcare systems data from the different databases/countries were not pooled. For this final report, data from the 4th wave observation period covered patients' data from the previous three waves.

The statistical analysis was conducted using the SAS® software V9.2 or later Windows™ (SAS Institute, North Carolina, US).

9.9.1. Main summary measures

The statistical analyses were descriptive in nature, using univariate descriptive methods with no statistical inference.

- Continuous variables are described by their number (of valid cases, of missing values), mean, standard deviation, and median, Q1, Q3, minimum, and maximum
- Categorical variables are described as the total number of valid cases and of missing values and relative percentage for each category, the denominator being the number of valid cases
- Confidence intervals of 95% were calculated, when relevant

9.9.2. Main statistical methods

The study characteristics are described overall for patients initiated with dulaglutide and in the subgroups of interest corresponding to dulaglutide initiators. Some characteristics of dulaglutide initiators were described at both the index date and the baseline period, for example, concomitant medications were defined as those prescriptions recorded at the index date of dulaglutide initiation (or within at least 90 days prior to), while medication history was defined as those medications which were recorded during the 6-month baseline period prior to dulaglutide initiation. Note that subgroups were not mutually exclusive: a patient could be part of more than one subgroup (for example, elderly patients ≥75 years and with hepatic disease).

9.9.3. Missing values

For each descriptor, the number and percent of patients with missing data were indicated. There was no replacement or imputation of missing data. Missing values were not taken into account in the denominator for the calculation of percentages.

9.9.4. Amendments to the statistical analysis plan

No amendments were made to the Statistical analysis plan (SAP).

9.10. Quality control

The secondary databases used for this study are widely utilised for research and have data collection processes in place that are in accordance with local and European law. The study programs for data management or statistical analyses were dual validated by two individuals to ensure data integrity and accuracy.

The project team followed all the corporate IQVIA SOPs in line with conducting observational and safety studies as well as Eli Lilly and IQVIA's Quality agreement. All the project documents, including Study protocol and SAP, were approved by the client before data extraction as per the SOPs. As the internal quality review of deliverables is part of corporate SOPs of IQVIA, hence all intermediate and final deliverables were reviewed by one or more subject matter experts.

In addition to the above process, and upon Eli Lilly's request, IQVIA has documented, and provided back to Eli Lilly, a quality review by a qualified individual external to the writing team of all final deliverables (for example, interim and final reports, abstracts, posters, manuscripts) to include the following:

1. Confirm that the source of the data and/or results has been documented and that results, and data have been checked by comparison to the source
2. Check the internal consistency of the medical research data presented in the document
3. Confirm that the conclusions are accurate, objective, balanced, and consistent with other published or released results
4. Confirm that the format and content of the document are aligned with applicable external requirements
5. Final annotated version of any disclosures (abstracts, posters and manuscripts)

10. Results

10.1. Participants

For this final report of the dulaglutide utilisation study, the utilisation profile of dulaglutide among populations of interest is described in the following sections for France, Germany, Spain, Sweden and the UK. Detailed analysis of dulaglutide utilisation such as medication use characteristics, including medication errors (i.e., prescribing dulaglutide to patients with T2DM in >1 weekly dose) and off-label use (i.e., prescribing dulaglutide to patients without diagnosis of T2DM, or prescribing dulaglutide as first-line therapy to patients with T2DM) is also described in this final report.

Dulaglutide received marketing authorisation throughout the EU in November 2014 and became available in EU countries beginning January 2015. Between January 2015 and December 2017, a total of 15,619 dulaglutide initiators were eligible for analyses, corresponding to 5,456 in Sweden; 4,759 in Germany; 2,716 in Spain; 1,384 in France; and 1,304 in the UK (Table 9.9.4-1).

Table 9.9.4-1 Distribution of dulaglutide initiators by country

Populations of Interest	France N (%)	Germany N (%)	Spain N (%)	Sweden N (%)	UK N (%)
Patient initiated with Dulaglutide*	1,384 (100)	4,759 (100)	2,716 (100)	5,456 (100)	1,304 (100)
Patients with T2DM	1,317 (95.2)	4,759 (100)	2,673 (98.4)	5,373 (98.5)	1,304 (100)
Age available*	1,384 (100)	4,759 (100)	2,716 (100)	5,456 (100)	1,304 (100)
Gender available*	1,384 (100)	4,759 (100)	2,716 (100)	5,456 (100)	1,304 (100)
BMI available*	457 (33)	2,667 (56)	2,468 (90.9)	-	1,167 (89.5)
Weight available*	880 (63.6)	2,698 (56.7)	2,475 (91.1)	-	1,174 (90.0)
Height available*	529 (38.2)	2,753 (57.8)	2,674 (98.5)	-	669 (51.3)
Severe renal failure*	none	26 (0.5)	36 (1.3)	27 (0.5)	PPD
Heart failure*	21 (1.5)	503 (10.6)	178 (6.6)	392 (7.2)	42 (3.2)
Hepatic disease*	PPD	151 (3.2)	451 (16.6)	103 (1.9)	100 (7.7)
Severe gastrointestinal disease*	68 (4.9)	386 (8.1)	287 (10.6)	471 (8.6)	234 (17.9)
Women, of which *	628 (45.4)	2,129 (44.7)	1,361 (50.1)	2,222 (40.7)	613 (47)
Pregnant women*	none	PPD			PPD
Breast-feeding women*	none	none	none	none	none

* Derived variable
BMI: body mass index; T2DM: type 2 diabetes mellitus; UK: United Kingdom
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated.
Source: Interim Statistical Dataset France, Table T_01; Germany, Table T_01; Spain, Table T_01; Sweden, Table T_01; UK, Table T_01

10.1.1. France

During the study period, a total of 1,384 dulaglutide initiators were identified in the French IQVIA DA database. A majority of those patients were diagnosed with T2DM (95.2%). Demographic details were available for all patients; however, information for weight, height, and BMI was not available for all patients. Among the patients who started dulaglutide 45.4% were

women, and none were pregnant or breast-feeding at the time of dulaglutide initiation. None of the 1,384 patients who started treatment with dulaglutide had a history of severe renal failure. Few patients had histories of hepatic disease or heart failure (PPD and 1.5%, respectively). Approximately 5% of the patients had a diagnosis indicative of severe GI disease.

10.1.2. Germany

During the study period, a total of 4,759 dulaglutide initiators were identified in the German IQVIA DA database. All patients were diagnosed with T2DM, and all had demographic details. More than half of the patients had height, weight, and BMI information. About 45% of dulaglutide initiators were women. Of these, PPD were pregnant and none were breast-feeding at the time of initiating dulaglutide treatment and hence, for privacy norms, no subgroup data for pregnant women are presented in the report. A small number of patients had a history of severe renal failure (0.5%). The proportions of patients with histories of heart failure, severe GI disease, and hepatic disease were 10.6%, 8.1%, and 3.2%, respectively.

10.1.3. Spain

During the study period, a total of 2,716 dulaglutide initiators were identified in the SIDIAP database. Among patients initiating dulaglutide, 98.4% were diagnosed with T2DM, and all had demographic information available in the database. The majority of dulaglutide initiators had height, weight, and BMI details. Half of the patients were women (50.1%), of which PPD were pregnant and none were breast-feeding at the time of dulaglutide initiation and hence, for privacy norms, no subgroup data for pregnant women are presented in the report. Among dulaglutide initiators, 1.3% had a history of severe renal failure. The proportions of patients with histories of hepatic disease, severe GI disease, and heart failure were 16.6%, 10.6%, and, 6.6%, respectively.

10.1.4. Sweden

During the study period, a total of 5,456 dulaglutide initiators were identified in the Swedish NPR and SPDR database. The vast majority of those patients (98.5%) were diagnosed with T2DM, and all had demographic information available. About 40.7% of dulaglutide initiators were women. Of these, PPD women were pregnant and none were breast-feeding at the time of starting dulaglutide treatment and hence, for data protection norms, no subgroup data for pregnant women are presented in the report. A small number of patients had a history of severe renal failure (0.5%). The proportions of patients with histories of severe GI disease, heart failure, and hepatic disease were 8.6%, 7.2%, and 1.9%, respectively. Information on height, weight, and BMI is not available in the NPR.

10.1.5. UK

During the study period, a total of 1,304 dulaglutide initiators were identified in the CPRD database. All patients were diagnosed with T2DM, and all had demographic information available. The vast majority of dulaglutide initiators had height, weight, and BMI details. Forty seven percent of dulaglutide initiators were women, of which PPD were pregnant and none were breast-feeding at the time of dulaglutide initiation and hence, for privacy norms, no subgroup data for pregnant women are presented in the report. Similarly, PPD of dulaglutide initiators had a

history of severe renal failure hence, no subgroup analysis results on severe renal failure have been presented. The proportions of patients with histories of severe GI disease, hepatic failure, and heart failure were 17.9%, 7.7%, and 3.2%, respectively.

10.2. Descriptive Data

10.2.1. Overall

10.2.1.1. Demographics and Populations of Interest

The characteristics of dulaglutide initiators across the study countries are summarised in Table 10.2.1-1. The mean age of dulaglutide initiators ranged from 57 years in the UK to 62 years in France. Overall, more than one-third of the dulaglutide initiators were elderly (≥65 years of age). Patients aged ≥75 years comprised about 10% of dulaglutide initiators in all countries, except in the UK (4.7%). Except for Spain, most of dulaglutide initiators in other countries were males.

Few patients were reported to have pre-existing severe renal failure in most countries (1.6% in Spain, 0.5% in Germany and Sweden, and PPD patients in the UK). History of severe renal failure was not identified among dulaglutide initiators in France. The distribution of patients with disease histories of interest across studied countries were: hepatic disease (16.6% in Spain, 7.7% in UK, 3.2% in Germany, 1.9% in Sweden, and PPD in France), severe GI disease (17.9% in UK, 10.6% in Spain, 8.6% in Sweden, 8.1% in Germany, and 4.9% in France), and heart failure (10.6% in Germany, 7.2% in Sweden, 6.6% in Spain, 3.2% in UK, and 1.5% in France). Among women treated with dulaglutide, 5 women in Germany, 2 women each in Spain, Sweden, and UK were pregnant but none were breast-feeding at the time of starting treatment with dulaglutide.

The mean duration of diabetes varied among first-time users of dulaglutide, with relatively shorter duration observed in Germany and France (4-5 years), compared to a longer duration in Spain, Sweden and the UK (8-10 years). With the exception of patients in Spain, the duration of diabetes treatment appeared to be consistent with the duration of underlying diabetes. Compared to a mean diabetes duration of about 10 years, the mean duration of treatment was approximately 5 years in Spanish dulaglutide initiators. The average weekly dose was 1.4 mg in Spain; 1.3 mg in Germany, Sweden, and the UK, and 0.8 mg in France.

Table 10.2.1-1 Description of dulaglutide initiators by country

Description	France (N=1,384)	Germany (N=4,759)	Spain (N=2,716)	Sweden (N=5,456)	UK (N=1,304)
Age (range)*					
0-4 years	none	none	none	none	none
5-9 years	none	none	none	none	none
10-14 years	none	none	none	none	none
15-17 years	PPD	none	none	PPD	none
18-44 years	PPD	400 (8.4%)	244 (9%)	486 (8.9%)	146 (11.2%)

Description	France (N=1,384)	Germany (N=4,759)	Spain (N=2,716)	Sweden (N=5,456)	UK (N=1,304)
45-64 years	724 (52.3%)	2,701 (56.8)	1,518 (55.9%)	2,852 (52.3%)	795 (61%)
65-74 years	441 (31.9%)	1,174 (24.7%)	741 (27.3%)	1,588 (29.1%)	302 (23.2%)
≥ 75 years	133 (9.6%)	484 (10.2%)	213 (7.8%)	PPD	61 (4.7%)
Mean (SD)	61.6 (10.7)	59.8 (11.27)	59.7 (10.8)	60.2 (11.7)	57.4 (11.0)
Min-Max	17 - 93	20 - 92	19 - 91	16 - 95	20 - 92
Median [Q1-Q3]	62 [55 - 69]	60 [53 - 67]	60 [53 - 67]	61 [53 - 69]	58 [50 - 65]
Height (cm)					
N	529	2,753	2,674	none	669
Mean (SD)	167.1 (10.2)	171.7 (9.7)	161.6 (11.6)	-	168.7 (10.2)
Min-Max	140 - 200	145 - 200	130 - 196	-	137 - 197
Median [Q1-Q3]	167 [160 - 175]	172 [164 - 179]	162 [154.2 - 170.0]	-	169 [160 - 177]
Missing	855 (61.8%)	2,006 (42.2%)	42 (1.6%)	5,456 (100%)	635 (48.7%)
Weight (kg)					
N	880	2,698	2,475	none	1,174
Mean (SD)	94.1 (19.5)	107.8 (22.6)	98.7 (18.5)	-	105.9 (22.8)
Min-Max	42 - 180	48.8-200	35.5 - 189	-	41.4 - 198
Median [Q1-Q3]	92 [81 - 106]	105 [92-121.4]	97 [85.9 - 109]	-	104 [90 - 119]
Missing	504 (36.4%)	2,061 (43.3%)	241 (8.9%)	5,456 (100%)	130 (10%)
Severe renal failure*	none	26 (0.5%)	36 (1.3%)	27 (0.5%)	4 (0.3%)
Hepatic disease*	PPD	151 (3.2%)	451 (16.6%)	103 (1.9%)	100 (7.7%)
Severe GI disease*	68 (4.9%)	386 (8.1%)	287 (10.6%)	471 (8.6%)	234 (17.9%)
Heart failure*	21 (1.5%)	503 (10.6%)	178 (6.6%)	392 (7.2%)	42 (3.2%)
Pregnant women*	none	PPD			
Gender					
Male	756 (54.6%)	2,630 (55.3%)	1,355 (49.9%)	3,234 (59.3%)	691 (53%)
Female	628 (45.4%)	2,129 (44.7%)	1,361 (50.1%)	2,222 (40.7%)	613 (47%)
T2DM duration: time since diagnosis					
N	1,317	4,759	2,673	5,373	1,304
≤ 1 year	102 (7.7%)	544 (11.4%)	213 (8%)	310 (5.8%)	78 (6%)
1 – 5 years	763 (57.9%)	2,195 (46.1%)	420 (15.7%)	1,166 (21.7%)	180 (13.8%)
6 – 10 years	452 (34.3%)	1,353 (28.4%)	737 (27.6%)	1,656 (30.8%)	407 (31.2%)
> 10 years	none	667 (14%)	1,303 (48.7%)	2,241 (41.7%)	639 (49%)
Mean (SD)	4.1 (2.4)	5.2 (4)	9.8 (6.2)	8.2 (4.5)	10.4 (6.4)
Min-Max	0 - 8.8	0 - 24.8	0 - 47.1	0 - 20.7	0 - 52
Median [Q1-Q3]	3.5 [2.2 - 6.3]	4.2 [2.0 - 7.6]	9.9 [5.1 - 13.3]	8.6 [4.6 - 11.4]	9.8 [6.0 - 14.2]

Description	France (N=1,384)	Germany (N=4,759)	Spain (N=2,716)	Sweden (N=5,456)	UK (N=1,304)
Missing	67 (4.8%)	none	43 (1.6%)	83 (1.5%)	none
Duration of T2DM treatment					
N	1,316	4,759	2,501	5,348	1,304
≤ 1 year	112 (8.5%)	1,033 (21.7%)	282 (11.3%)	307 (5.7%)	76 (5.8%)
1 - 5 years	766 (58.2%)	2,101 (44.1%)	1,249 (49.9%)	1,218 (22.8%)	305 (23.4%)
> 5 years	438 (33.3%)	1,625 (34.1%)	970 (38.8%)	3,823 (71.5%)	923 (70.8%)
Mean (SD)	4.1 (2.4)	4.2 (3.7)	4.6 (3.2)	7.6 (3.7)	8.7 (5.4)
Min-Max	0 - 8.8	0 - 24.8	0 -16.2	0 - 12.5	0 - 27.7
Median [Q1-Q3]	3.5 [2.1 - 6.2]	3.3 [1.2 - 6.3]	3.9 [2.2 - 6.7]	8.4 [4.5 - 10.9]	8.3 [4.5 - 12.3]
Missing	68 (4.9%)	none	215 (7.9%)	108 (2%)	none
Dulaglutide average weekly dose (mg/week)*					
N	986	3,687	1,630	4,828	1,304
Mean (SD)	0.8 (0.5)	1.3 (0.4)	1.4 (0.2)	1.3 (0.3)	1.3 (0.3)
Min-Max	0 - 3.0	0 - 3.0	0.8-1.5	0.1 - 4.6	0.8 - 1.5
Median [Q1-Q3]	0.6 [0.4 - 1.1]	1.4 [1.0 - 1.5]	1.5 [1.5 - 1.5]	1.5 [1.2 - 1.5]	1.5 [1.1 - 1.5]
Missing	398 (28.8%)	1072 (22.5%)	1086 (40%)	628 (11.5%)	none

* Derived variable
GI: gastrointestinal; SD: standard deviation; T2DM: type 2 diabetes mellitus; UK: United Kingdom
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Germany, Table T_03; France, Table T_03; Spain, Table T_03, Sweden, Table T_03; UK, Table T_03.

10.2.1.2. Comorbidities and Concomitant Medications

Clinical characteristics of dulaglutide initiators in the study countries are summarised in Table 10.2.1-2. The majority of patients who started treatment with dulaglutide had pre-existing hypertension and dyslipidaemia (France: 80% and 73%, Germany: 60% each, Spain: 73% and 61%, Sweden: 85% and 82%, and UK: 60% and 27%). With the exception of patients in Spain, the majority of dulaglutide initiators had macrovascular complications as comorbidities (19% in Spain vs. 80% in France, 67% in Germany, 83% in Sweden, and 81% in the UK), with ischaemic heart disease making up the largest proportion of macrovascular complications across all study countries. Conversely, microvascular complications were observed, overall, to be proportionately less prevalent (46% in Germany, 35% in the UK, 23% in Sweden, 20% in Spain, and 4% in France). The distribution of specific microvascular complications of interest was observed to be inconsistent across countries. Diabetic retinopathy accounted for most of the microvascular complications in the UK (33.6%), Sweden (19.8%), and Spain (16.3%); whereas diabetic neuropathy accounted for the preponderance of these complications in Germany (36.9%) and France (3%). Overall, between 1-3% of dulaglutide initiators had histories for solid tumours, with 0.5% to1.4% affecting the breast.

Across study countries, the vast majority of dulaglutide initiators were previously treated with other ADMs—within 6 months before dulaglutide initiation (97% in Sweden, 87% in the UK,

85% in Spain, 83% in Germany, and 78% in France), including at index date of dulaglutide initiation (94% in France, 92% in Sweden, 76% in Spain and the UK each, and 47% in Germany). Among previous ADMs, biguanides, accounted for most of the concomitant medications in France (53%), Sweden (75%) and the UK (63%), whereas insulins contributed the highest proportion of concomitant ADMs in Germany (53%) and Spain (35%). At index date, biguanides accounted for the majority of concurrent ADMs in France (76%), Sweden (61%) the UK (53%), and Spain (40.0%). Approximately 28% of patients in Germany were prescribed insulins upon dulaglutide initiation. Use of sulfonylureas/sulphonamides was as follows: 41.9% in France, 33.8% in the UK, 18.6% in Spain, 17.8% in Sweden, and 5.2% in Germany.

Off-label use of dulaglutide (defined by prescribing dulaglutide to patients without diagnosis of T2DM, or prescribing dulaglutide as first-line therapy to patients with T2DM) was low across study countries. In France, up to 22.3% were prescribed dulaglutide as first-line therapy; however, only 4.8% of dulaglutide initiators were not diagnosed with T2DM at the time of dulaglutide initiation. Up to 15.1% of dulaglutide initiators in Spain, and up to 2.9% of those in Sweden were prescribed dulaglutide as first-line therapy; nonetheless, only 1.6% of patients in Spain and 1.5% of those in Sweden were not diagnosed with T2DM at the time of dulaglutide initiation. Prescribing dulaglutide as first-line therapy among patients with T2DM was up to 17.2% in Germany, and up to 12.9% in the UK; however, all dulaglutide initiators in Germany and the UK were diagnosed with T2DM at the time of dulaglutide prescribing (Tables 9.9.4-1 and 10.2.1-2).

Dulaglutide was initially prescribed in >1 weekly dose to 84.3% of patients in the UK, and 5% and 0.2% of patients in France and Sweden respectively. In Germany and Spain, dulaglutide initiation was in once weekly doses.

Table 10.2.1-2 Description of comorbidities and co-medications among dulaglutide initiators by country

Description	France (N=1,384)	Germany (N=4,759)	Spain (N=2,716)	Sweden (N=5,456)	UK (N=1,304)
Comorbidities*,†					
Hypertension	1,102 (79.6%)	2,875 (60.4%)	1,972 (72.6%)	4,636 (85%)	776 (59.5%)
Dyslipidaemia	1,011 (73%)	2,852 (59.9%)	1,643 (60.5%)	4,447 (81.5%)	350 (26.8%)
Obesity status (by BMI)					
N	457	2,667	2,468	-	1,167
<18.5 kg/m²	none	PPD		-	none
18.5-24.9 kg/m²	20 (4.4%)	PPD	PPD	-	19 (1.6%)
25.0-29.9 kg/m²	95 (20.8%)	354 (13.3%)	180 (6.6%)	-	130 (11.1%)
30.0-34.9 kg/m²	160 (35%)	821 (30.8%)	869 (32%)	-	363 (31.1%)
≥35.0 kg/m²	182 (39.8%)	1442 (54.1%)	1398 (51.5%)	-	655 (56.1%)
Mean (SD)	34.1 (6.1)	36.5 (6.6)	38.6 (10.6)	-	37 (7.1)
Min-Max	19.4 - 60.5	16.3 - 61.4	12-77.2	-	20.9 - 80.6
Median [Q1-Q3]	33.7 [30 - 37.5]	35.6 [31.8 - 40.4]	35.8 [32.4-40.2]	-	36 [32.2 - 41]

Description	France (N=1,384)	Germany (N=4,759)	Spain (N=2,716)	Sweden (N=5,456)	UK (N=1,304)
Missing	927 (67%)	2,092 (44%)	248 (9.1%)	5,456 (100%)	137 (10.5%)
Macrovascular complications *	1,110 (80.2%)	3,209 (67.4%)	508 (18.7%)	4,542 (83.2%)	1,052 (80.7%)
Ischaemic heart disease	1,110 (80.2%)	3,091 (65%)	354 (13%)	4,523 (82.9%)	1,051 (80.6%)
Stroke	PPD	176 (3.7%)	70 (2.6%)	306 (5.6%)	26 (2%)
Peripheral arterial obstructive disease	PPD	452 (9.5%)	148 (5.4%)	148 (2.7%)	24 (1.8%)
Microvascular complications	53 (3.8%)	2,206 (46.4%)	529 (19.5%)	1,260 (23.1%)	462 (35.4%)
Diabetic neuropathy	42 (3%)	1,754 (36.9%)	PPD	250 (4.6%)	PPD
Diabetic retinopathy	PPD	447 (9.4%)	443 (16.3%)	1,080 (19.8%)	438 (33.6%)
Diabetic nephropathy	PPD	814 (17.1%)	PPD	188 (3.4%)	PPD
Solid tumours	PPD	97 (2%)	93 (3.4%)	107 (2%)	19 (1.5%)
Liver	none	none	none	PPD	none
Pancreas	0 (0.0%)	PPD	PPD	PPD	
Endometrium	PPD	PPD	12 (0.4%)	PPD	
Colon	PPD	22 (0.5%)	17 (0.6%)	27 (0.5%)	PPD
Rectum	none	PPD	PPD	13 (0.2%)	PPD
Breast	PPD	44 (0.9%)	38 (1.4%)	41 (0.8%)	PPD
Bladder	PPD	14 (0.3%)	25 (0.9%)	24 (0.4%)	PPD
Concomitant ADM during 6-month baseline*	1,075 (77.7%)	3,939 (82.8%)	2,306 (84.9%)	5,299 (97.1%)	1,136 (87.1%)
Insulins	232 (16.8%)	2,502 (52.6%)	943 (34.7%)	2,408 (44.1%)	24 (1.8%)
Biguanides	726 (52.5%)	1,769 (37.2%)	850 (31.3%)	4,113 (75.4%)	823 (63.1%)
Sulfonylureas/ Sulfonamides[1]	580 (41.9%)	246 (5.2%)	505 (18.6%)	971 (17.8%)	441 (33.8%)
Alpha-glucosidase inhibitors	25 (1.8%)	21 (0.4%)	PPD	29 (0.5%)	PPD
Thiazolidinediones	0 (0.0%)	21 (0.4%)	PPD	150 (2.7%)	84 (6.4%)
Dipeptidyl peptidase-4 inhibitors	168 (12.1%)	599 (12.6%)	291 (10.7%)	1,510 (27.7%)	371 (28.5%)
Sodium glucose cotransporter-2 inhibitors	none	837 (17.6%)	290 (10.7%)	976 (17.9%)	421 (32.3%)
GLP-1 RAs (other than dulaglutide)*	258 (18.6%)	620 (13.0%)	450 (16.6%)	999 (18.3%)	90 (6.9%)
Meglitinides	177 (12.8%)	79 (1.7%)	152 (5.6%)	239 (4.4%)	2 (0.2%)
Single pill combinations of ADM	325 (23.5%)	751 (15.8%)	821 (30.2%)	321 (5.9%)	26 (2%)

Description	France (N=1,384)	Germany (N=4,759)	Spain (N=2,716)	Sweden (N=5,456)	UK (N=1,304)
Single injection combination of insulin and GLP-1 RA	none	165 (3.5%)	none	33 (0.6%)	PPD
Concomitant ADM at index date*	1,307 (94.4%)	2,242 (47.1%)	2,058 (75.8%)	5,003 (91.7%)	985 (75.5%)
Insulins	291 (21%)	1,321 (27.8%)	878 (32.3%)	2,182 (40%)	PPD
Biguanides	1,057 (76.4%)	1,026 (21.6%)	1,073 (39.5%)	3,351 (61.4%)	686 (52.6%)
Sulfonylureas / Sulfonamides[1]	701 (50.7%)	59 (1.2%)	298 (11%)	724 (13.3%)	365 (28%)
Alpha-glucosidase inhibitors	22 (1.6%)	PPD	none	20 (0.4%)	PPD
Thiazolidinediones	none	PPD	31 (1.1%)	127 (2.3%)	62 (4.8%)
Dipeptidyl peptidase-4 inhibitors	124 (9%)	77 (1.6%)	93 (3.4%)	1,100 (20.2%)	265 (20.3%)
Sodium glucose cotransporter-2 inhibitors	none	258 (5.4%)	92 (3.4%)	768 (14.1%)	316 (24.2%)
GLP-1 RAs (other than dulaglutide)	137 (9.9%)	17 (0.4%)	27 (1%)	741 (13.6%)	12 (0.9%)
Meglitinides	197 (14.2%)	15 (0.3%)	83 (3.1%)	194 (3.6%)	PPD
Single pill combinations of ADM	245 (17.7%)	97 (2%)	373 (13.7%)	238 (4.4%)	13 (1%)
Single injection combination of insulin and GLP-1 RA	none	PPD	none	28 (0.5%)	none
Medication error‡	49 (5%)	none	none	PPD	1,099 (84.3%)

* Derived variable
‡ Patients with dulaglutide prescribed >1 dose per week are considered as medication errors.
ADM: anti-diabetes medication; BMI: body mass index; GI: gastrointestinal; GLP-1 RA: glucagon-like peptide 1 receptor agonist; SD: standard deviation; T2DM: type 2 diabetes mellitus; UK: United Kingdom
[1]ATC codes A10BB (Sulfonylureas) and A10BC (Sulfonamides - heterocyclic) have been placed under Sulfonylureas/Sulfonamides
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Germany, Table T_03; France, Table T_03; Spain, Table T_03, Sweden, Table T_03; UK, Table T_03.

10.2.2. By Populations of Interest

10.2.2.1. Demographics and Populations of Interest

10.2.2.1.1. France

In France, a total of 1,384 patients with T2DM started treatment with dulaglutide. The details of the overall population in France are presented in Table 10.2.2-1. Overall, most of the dulaglutide initiators were within the age group of 45-64 years (52.3%), followed by 65-74 years (31.9%). A similar trend was observed among patients with pre-existing severe GI disease in which the

highest proportion of patients were of 45-64 years of age (42.6%), followed by 65-74 years (33.8%). In contrast, most patients with heart failure were within 65-74 years of age (38.1%), followed by 45-64 years of age (28.6%). The mean age of patients with previous heart failure and history of severe GI disease was higher than that of the overall population (66.9 years and 62.9 years vs. 61.6 years, respectively). The gender distribution was different from that of all dulaglutide initiators in France and among subgroups; most of the patients overall and with previous heart failure were male (54.6% and 66.7%, respectively) while a majority of elderly (≥75 years of age) patients (53.4%) and patients with pre-existing severe GI disease (55.9%) were female.

The disease characteristics varied among the three subgroups, with an average of 4.6-5.6 years since T2DM diagnosis and 4.6-5.5 years of T2DM treatment duration, which was higher than that among the overall population (4.1 years since T2DM diagnosis and treatment duration). Compared to other subgroups of interest, patients with pre-existing heart failure had the highest average weekly dose of 1.2 mg/week. The average prescribed weekly dose of dulaglutide was similar across other subgroups of interest, and the overall study population (0.7-0.8 mg/week).

Table 10.2.2-1 Description of dulaglutide initiators per subgroup in France

	France All patients (N=1,384)	**Heart failure (N=21)**	**Severe GI disease (N=68)**	**Aged ≥75 (N=133)**
Age (range)*				
0-4 years	none	none	none	none
5-9 years	none	none	none	none
10-14 years	none	none	none	none
15-17 years	PPD	none	none	none
18-44 years	PPD	PPD		none
45-64 years	724 (52.3%)	PPD	29 (42.6%)	none
65-74 years	441 (31.9%)	PPD	23 (33.8%)	none
≥75 years	133 (9.6%)	PPD	PPD	133 (100%)
Mean (SD)	61.6 (10.7)	66.9 (13.1)	62.9 (11.4)	79.4 (3.8)
Min-Max	17 - 93	42 – 93	25 – 86	75 – 93
Median [Q1-Q3]	62 [55 - 69]	68 [61 - 72]	64 [56 - 70]	79 [76 - 82]
Children and adolescents*	PPD	none	none	none
Height (cm)				
N	529	9	27	46
Mean (SD)	167.1 (10.2)	165.9 (10.3)	165 (8.5)	162.6 (10.7)
Min-Max	140 - 200	140 – 175	147 – 185	147 – 187
Median [Q1-Q3]	167 [160 - 175]	170 [165 - 171]	165 [159 - 169]	162 [154 - 170]
Missing	855 (61.8%)	12 (57.1%)	41 (60.3%)	87 (65.4%)

	France All patients (N=1,384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
Weight (kg)				
N	880	13	41	77
Mean (SD)	94.1 (19.5)	103.8 (22.5)	94.3 (18.8)	86.7 (17.4)
Min-Max	42 - 180	74 - 154	59 - 139	42 - 130
Median [Q1-Q3]	92 [81 - 106]	97.7 [90 - 115.5]	94 [82 - 111]	88 [73 - 95.5]
Missing	504 (36.4%)	8 (38.1%)	27 (39.7%)	56 (42.1%)
Severe renal failure*	-	PPD	none	none
Hepatic disease*	PPD	PPD	PPD	PPD
Severe GI disease*	68 (4.9%)	none	68 (100%)	PPD
Heart failure*	PPD	21 (100%)	none	PPD
Pregnant women*	none	none	none	none
Gender				
Male	756 (54.6%)	PPD	30 (44.1%)	62 (46.6%)
Female	628 (45.4%)	PPD	38 (55.9%)	71 (53.4%)
T2DM duration: time since diagnosis				
N	1,317	19	67	129
≤ 1 year	102 (7.7%)	PPD		
1 - 5 years	763 (57.9%)	PPD	27 (40.3%)	71 (55%)
6 – 10 years	452 (34.3%)	PPD	39 (58.2%)	52 (40.3%)
>10 years	none	none	none	none
Mean (SD)	4.1 (2.4)	5.3 (2.3)	5.6 (2.2)	4.6 (2.4)
Min-Max	0 - 8.8	0.8 - 8.4	0.9 - 8.8	0.2 - 8.5
Median [Q1-Q3]	3.5 [2.2 - 6.3]	5.3 [3.8 - 7.5]	5.8 [3.8 - 7.3]	4.1 [2.7 - 7.1]
Missing	67 (4.8%)	2 (9.5%)	1 (1.5%)	4 (3%)
Duration of T2DM treatment				
N	1,316	21	67	128
≤ 1 year	112 (8.5%)	PPD		
1 - 5 years	766 (58.2%)	PPD	PPD	73 (57%)
> 5 years	438 (33.3%)	PPD	39 (58.2%)	PPD
Mean (SD)	4.1 (2.4)	4.8 (2.6)	5.5 (2.2)	4.6 (2.4)
Min-Max	0 - 8.8	0.6 - 8.4	0.2 - 8.8	0.2 - 8.5
Median [Q1-Q3]	3.5 [2.1 - 6.2]	4 [3.4 - 7.5]	5.8 [3.8 - 7.3]	4.2 [2.7 - 7]
Missing	68 (4.9%)	none	1 (1.5%)	5 (3.8%)
Dulaglutide average weekly dose (mg/week)*				

	France All patients (N=1,384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
N	986	16	52	104
Mean (SD)	0.8 (0.5)	1.2 (0.7)	0.8 (0.5)	0.7 (0.4)
Min-Max	0 - 3.0	0.2 - 3.0	0.2 - 3.0	0.1 - 2.0
Median [Q1-Q3]	0.6 [0.4 - 1.1]	1.2 [0.8 - 1.5]	0.6 [0.4 - 1.0]	0.6 [0.4 - 1.0]
Missing	398 (28.8%)	5 (23.8%)	16 (23.5%)	29 (21.8%)

* Derived variable
GI: gastrointestinal; SD: standard deviation; T2DM: type 2 diabetes mellitus;
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Subgroup of patients with hepatic disease has not been presented due to privacy morns (i.e. N<10)
Source: Interim Statistical Dataset France, Table T_06

10.2.2.1.2. Germany

In Germany, a total of 4,759 patients with T2DM started treatment with dulaglutide. The details of the overall population in Germany are presented in Table 10.2.2-2. Overall, most patients were within 45-64 years of age (56.8%) with a similar trend observed among patients with histories of heart failure (40.4%), hepatic (59.6%) or severe GI disease (46.6%), whereas most of the patients with severe renal failure were within 65-74 years of age (46.2%). The mean age of patients with severe renal failure (71.6 years), pre-existing heart failure (66.3 years), and severe GI disease (62.7 years) was higher than that of the overall population (59.8 years) and patients with hepatic disease (59.7 years). The gender distribution was comparable among the overall dulaglutide initiators in Germany and the subgroups; most of the patients overall (55.3%), with severe renal failure (53.8%), heart failure (61.6%), hepatic disease (62.3%) or severe GI disease (52.8%) were male, however, a majority of elderly (≥75 years of age) patients (51.9%) were female.

The disease characteristics were similar among the five subgroups, with an average of 6.1-7 years since T2DM diagnosis and 4.4-5.7 years of T2DM treatment duration, which was higher than that among the overall population (time since T2DM diagnosis: 5.2 years; T2DM treatment duration: 4.2 years). There was no considerable difference in the average weekly dose of dulaglutide among all the subgroups of interest, and overall the study population (1.1-1.3 mg/week).

Table 10.2.2-2 Description of dulaglutide initiators per subgroup in Germany

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Age (range)*						
0-4 years	none	none	none	none	none	none
5-9 years	none	none	none	none	none	none
10-14 years	none	none	none	none	none	none

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
15-17 years	none	none	none	none	none	none
18-44 years	400 (8.4%)	none	PPD			none
45-64 years	2,701 (56.8%)	PPD	203 (40.4%)	90 (59.6%)	180 (46.6%)	none
65-74 years	1,174 (24.7%)	PPD	167 (33.2%)	32 (21.2%)	110 (28.5%)	none
≥75 years	484 (10.2%)	PPD	PPD	PPD	PPD	484 (100%)
Mean (SD)	59.8 (11.3)	71.6 (7.8)	66.3 (10.4)	59.7 (10.4)	62.7 (12.2)	78.5 (3.2)
Min-Max	20 – 92	51 – 83	31 – 90	29 - 81	23 – 92	75 - 92
Median [Q1-Q3]	60 [53 - 67]	71 [66 - 79]	66 [59 - 74]	60 [53 - 67]	64 [55 - 71]	78 [76 - 80]
Children and adolescents*	none	none	none	none	none	none
Height (cm)						
N	2,753	22	312	90	244	263
Mean (SD)	171.7 (9.7)	169.4 (9.1)	171.6 (9.8)	172 (9.8)	171.1 (9.2)	167.4 (8.8)
Min-Max	145 – 200	152 – 188	145 - 195	149 - 192	149 – 196	145 - 189
Median [Q1-Q3]	172 [164 - 179]	170 [163 - 176]	172 [164 - 179]	172 [165 - 179]	171 [164 - 178]	167 [160 - 174]
Missing	2,006 (42.2%)	4 (15.4%)	191 (38%)	61 (40.4%)	142 (36.8%)	221 (45.7%)
Weight (kg)						
N	2,698	21	307	89	241	260
Mean (SD)	107.8 (22.6)	95.7 (18.5)	111.2 (23.6)	107.8 (22.4)	104.2 (21.8)	94.8 (17.5)
Min-Max	48.8 - 200	70 - 133	58 - 183	66.6 - 177.8	56.6 - 185	48.8 - 156
Median [Q1-Q3]	105 [92 - 121.4]	92.6 [83 - 103]	109.6 [93.4 - 125]	106 [91.6 - 118]	102 [89 - 116]	93 [83 - 103]
Missing	2,061 (43.3%)	5 (19.2%)	196 (39%)	62 (41.1%)	145 (37.6%)	224 (46.3%)
Severe renal failure*	26 (0.5%)	26 (100%)	PPD	PPD	PPD	
Hepatic disease*	151 (3.2%)	PPD	33 (6.6%)	151 (100%)	19 (4.9%)	18 (3.7%)
Severe GI disease*	386 (8.1%)	PPD	76 (15.1%)	19 (12.6%)	386 (100%)	71 (14.7%)
Heart failure*	503 (10.6%)	PPD	503 (100%)	33 (21.9%)	76 (19.7%)	124 (25.6%)
Pregnant women*	PPD	none	none	none	none	none

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Gender						
Male	2,630 (55.3%)	14 (53.8%)	310 (61.6%)	94 (62.3%)	204 (52.8%)	233 (48.1%)
Female	2,129 (44.7%)	12 (46.2%)	193 (38.4%)	57 (37.7%)	182 (47.2%)	251 (51.9%)
T2DM duration: time since diagnosis						
N	4,759	26	503	151	386	484
≤ 1 year	544 (11.4%)	none	26 (5.2%)	16 (10.6%)	27 (7%)	49 (10.1%)
1 - 5 years	2,195 (46.1%)	14 (53.8%)	186 (37%)	59 (39.1%)	120 (31.1%)	167 (34.5%)
6 – 10 years	1,353 (28.4%)	PPD	170 (33.8%)	47 (31.1%)	136 (35.2%)	142 (29.3%)
>10 years	667 (14%)	PPD	121 (24.1%)	29 (19.2%)	103 (26.7%)	126 (26%)
Mean (SD)	5.2 (4)	6.3 (4)	7 (4.7)	6.1 (4.5)	6.9 (4.5)	6.6 (4.8)
Min-Max	0 - 24.8	1.0 - 16.0	0 - 24.8	0 - 23.1	0 - 23.1	0 - 24.5
Median [Q1-Q3]	4.2 [2.0 - 7.6]	4.7 [3.4 - 8.9]	6 [3.2 - 9.8]	5 [2.8 - 8.9]	6.1 [3.4 - 10.4]	5.7 [2.5 - 10.2]
Missing	none	none	none	none	none	none
Duration of T2DM treatment						
N	4,759	26	503	151	386	484
≤ 1 year	1,033 (21.7%)	PPD	82 (16.3%)	30 (19.9%)	51 (13.2%)	116 (24%)
1 - 5 years	2,101 (44.1%)	13 (50%)	184 (36.6%)	58 (38.4%)	128 (33.2%)	158 (32.6%)
> 5 years	1,625 (34.1%)	PPD	237 (47.1%)	63 (41.7%)	207 (53.6%)	210 (43.4%)
Mean (SD)	4.2 (377)	4.4 (4.3)	5.5 (4.4)	4.9 (4.2)	5.7 (4.1)	5.1 (4.6)
Min-Max	0 - 24.8	0 - 16	0 - 24.8	0 - 23.1	0 - 23.1	0 - 24.5
Median [Q1-Q3]	3.3 [1.2 - 6.3]	3.6 [1.4 - 5.4]	4.8 [2.1 - 8.4]	4.1 [1.1 - 7.1]	5.3 [2.4 - 8.6]	4.1 [1.1 - 8.6]
Missing	none	none	none	none	none	none
Dulaglutide average weekly dose (mg/week)*						
N	3,687	23	395	123	297	364
Mean (SD)	1.3 (0.4)	1.1 (0.5)	1.2 (0.5)	1.3 (0.5)	1.3 (0.4)	1.3 (0.5)
Min-Max	0 - 3	0.1 - 1.8	0 - 3	0.2 - 3	0.1 - 3	0.1 - 3

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Median [Q1-Q3]	1.4 [1 - 1.5]	1.3 [0.9 - 1.4]	1.3 [0.9 - 1.5]	1.4 [1 - 1.5]	1.4 [1 - 1.5]	1.3 [0.9 - 1.5]
Missing	1,072 (22.5%)	3 (11.5%)	108 (21.5%)	28 (18.5%)	89 (23.1%)	120 (24.8%)

* Derived variable
GI: gastrointestinal; SD: standard deviation; T2DM: type 2 diabetes mellitus;
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Germany, Table T_06

10.2.2.1.3. Spain

In Spain, a total of 2,716 patients with T2DM started treatment with dulaglutide. The details of the overall population in Spain are presented in Table 10.2.2-3. Overall, most patients were within 45-64 years of age (55.9%) with a similar trend observed among patients with histories of hepatic disease (60.1%) and severe GI disease (47.4%), whereas most of the patients with histories of severe renal failure (41.7%) and heart failure (42.1%) were within 65-74 years of age. The mean age was lowest in patients with a history of hepatic disease (59.5 years). The gender distribution was different from that of all dulaglutide initiators in Spain and among subgroups. Overall, the gender distribution was comparable (male: 49.9%; female: 50.1%); however, among subgroups, most of the patients with pre-existing severe renal failure (61.1%), heart failure (57.3%), and severe GI disease (53.0%) were male; and those with hepatic disease (55.0%) and elderly (≥75 years of age) patients (63.4%) were mostly female.

The disease characteristics were similar among the five subgroups, with an average of 3.1-12.7 years since T2DM diagnosis and 4.6-5.9 years of T2DM treatment duration. The average weekly dose of dulaglutide was roughly equal across subgroups of interest, and overall the study population (1.3-1.4 mg/week).

Table 10.2.2-3 Description of dulaglutide initiators per subgroup in Spain

	Spain All patients (N=2,716)	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
Age (range)*						
0-4 years	none	none	none	none	none	none
5-9 years	none	none	none	none	none	none
10-14 years	none	none	none	none	none	none
15-17 years	none	none	none	none	none	none
18-44 years	244 (9%)	none	PPD	35 (7.8%)	12 (4.2%)	none
45-64 years	1,518 (55.9%)	PPD	PPD	271 (60.1%)	136 (47.4%)	none
65-74 years	741 (27.3%)	15 (41.7%)	75 (42.1%)	119 (26.4%)	100 (34.8%)	none

	Spain All patients (N=2,716)	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
≥ 75 years	213 (7.8%)	PPD	30 (16.9%)	26 (5.8%)	39 (13.6%)	213 (100%)
Mean (SD)	59.7 (10.8)	69.4 (9.2)	65.9 (9.2)	59.5 (9.8)	63.4 (10.4)	77.8 (2.9)
Min-Max	19 - 91	53 - 89	32 - 91	21 - 80	26 - 85	75 - 91
Median [Q1-Q3]	60 [53 - 67]	71 [62 - 76]	67 [60 - 73]	60 [53 - 66]	64 [57 - 72]	77 [75 - 79]
Children and adolescents*	none	none	none	none	none	none
Height (cm)						
N	2,674	36	176	450	285	212
Mean (SD)	161.6 (11.7)	161.8 (11.3)	159.9 (12.9)	160.9 (10.5)	161.3(11)	158.1 (9.6)
Min-Max	130 - 196	131.7 - 180	131.5 - 190	130 - 188	130 - 185	130 – 180
Median [Q1-Q3]	162 [154.2 - 170]	163 [156 - 170.5]	159.5 [150 - 170]	161 [155 - 168]	162 [154 - 169]	157 [151 - 165.3]
Missing	42 (1.6%)	none	2 (1.1%)	1 (0.2%)	2 (0.7%)	1 (0.5%)
Weight (kg)						
N	2,475	32	162	427	262	200
Mean (SD)	98.7 (18.5)	93.3 (14.1)	100.7 (19.5)	97.7 (17.9)	95.5 (17.1)	88.3 (14.1)
Min-Max	35.5 - 189	68.2 - 124.6	54.5 - 155	62 - 168	60 - 158	53.3 - 130
Median [Q1-Q3]	97 [85.9 - 109]	89.8 [83.5 - 105.8]	100 [87 - 111]	95 [84.7 - 108]	93.8 [83.3 - 105]	88 [78.8 - 96.9]
Missing	241 (8.9%)	4 (11.1%)	16 (9.0%)	24 (5.3%)	25 (8.7%)	13 (6.1%)
Severe renal failure*	36 (1.6%)	36 (100%)	12 (8.5%)	PPD	PPD	PPD)
Hepatic disease*	451 (16.6%)	PPD	24 (13.5%)	451 (100%)	65 (22.6%)	PPD
Severe GI disease*	287 (10.6%)	PPD	34 (19.1%)	65 (14.4%)	287 (100%)	39 (18.3%)
Heart failure*	178 (6.6%)	12 (33.3%)	178 (100%)	PPD	PPD	30 (14.1%)
Pregnant women*	2 (0.1%)	none	none	none	none	none
Breast-feeding women*	0 (0.0%)	none	none	none	none	none
Gender						
Male	1,355 (49.9%)	22 (61.1%)	102 (57.3%)	203 (45%)	152 (53%)	78 (36.6%)
Female	1,361 (50.1%)	14 (38.9%)	76 (42.7%)	248 (55%)	135 (47%)	135 (63.4%)
T2DM duration: time since diagnosis						
N	2,673	36	178	447	284	212
≤ 1 year	213 (8%)	PPD	PPD	24 (5.4%)	17 (6.0%)	PPD
1 – 5 years	420 (15.7%)	PPD	PPD	74 (16.6%)	31 (10.9%)	PPD
6 – 10 years	737 (27.6%)	PPD	44 (24.7%)	152 (34%)	65 (22.9%)	38 (17.9%)
>10 years	1,303 (48.7%)	26 (72.2%)	97 (54.5%)	197 (44.1%)	171 (60.2%)	160 (75.5%)
Mean (SD)	9.8 (6.2)	12.7 (6.1)	11 (6.7)	9.3 (5.2)	11 (6.2)	3.1 (5.9)
Min-Max	0 - 47.1	0 – 26	0 - 40.9	0 - 25.2	0 - 37.4	0 - 47.1

	Spain All patients (N=2,716)	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
Median [Q1-Q3]	9.9 [5.1 - 13.3]	12.7 [8.7 - 15.9]	10.6 [5.8 - 14.0]	8.9 [5.3 - 12.9]	11.3 [6.9 - 14.1]	13 [10.2 - 15.9]
Missing	43 (1.6%)	none	none	4 (0.9%)	3 (1%)	1 (0.5%)
Duration of T2DM treatment						
N	2,501	34	165	406	272	204
≤ 1 year	282 (11.3%)	PPD	PPD	37 (9.1%)	25 (9.2%)	PPD
1 - 5 years	1,249 (49.9%)	PPD	PPD	211 (52%)	137 (50.4%)	PPD
> 5 years	970 (38.8%)	17 (50%)	78 (47.3%)	158 (38.9%)	110 (40.4%)	103 (50.5%)
Mean (SD)	4.6 (3.2)	5.9 (3.4)	5.2 (3.1)	4.6 (3)	4.7 (3.3)	5.5 (3.3)
Min-Max	0 - 16.2	0 - 14.4	0 - 13.8	0 - 14.1	0 - 15.9	0 - 15.3
Median [Q1-Q3]	3.9 [2.2 - 6.7]	5.1 [2.8 - 9.1]	4.6 [2.6 - 7.8]	3.9 [2.3 - 6.7]	3.9 [1.9 - 6.9]	5.0 [2.8 - 8.3]
Missing	215 (7.9%)	2 (5.6%)	13 (7.3%)	45 (10%)	15 (5.2%)	9 (4.2%)
Dulaglutide average weekly dose (mg/week)*						
N	1,630	20	119	279	176	119
Mean (SD)	1.4 (0.2)	1.4 (0.3)	1.3 (0.3)	1.4 (0.2)	1.4 (0.2)	1.3 (0.3)
Min-Max	0.8 - 1.5	0.8 - 1.5	0.8 – 1.5	0.8 – 1.5	0.8 – 1.5	0.8 – 1.5
Median [Q1-Q3]	1.5 [1.5 - 1.5]	1.5 [1.5 - 1.5]	1.5 [1.4 - 1.5]	1.5 [1.5 - 1.5]	1.5 [1.5 - 1.5]	1.5 [1.3 - 1.5]
Missing	1,086 (40%)	16 (44.4%)	59 (33.2%)	172 (38.1%)	111 (38.7%)	94 (44.1%)

* Derived variable
GI: gastrointestinal; SD: standard deviation; T2DM: type 2 diabetes mellitus;
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Spain, Table T_06

10.2.2.1.4. Sweden

In Sweden, a total of 5,456 patients with T2DM started treatment with dulaglutide. The details of the overall population in Sweden are presented in Table 10.2.2-4. Overall, most patients were within 45-64 years of age (52.3%) with a similar trend observed among patients with histories of hepatic disease (58.3%) and severe GI disease (41.6%), whereas most of the patients with severe renal failure (51.9%) and heart failure (44.4%) were within 65-74 years of age. The mean age of patients with pre-existing heart failure (68.1 years), severe renal failure (67.0 years), and severe GI disease (64.2 years) was higher than that of the overall patient population (60.2 years) and patients with hepatic disease (57.7 years). The gender distribution was comparable among the overall dulaglutide initiators in Sweden and the subgroups; majority of the patients overall (59.3%), with histories of severe renal failure (55.6%), heart failure (67.3%), hepatic disease (61.2%) or patients ≥75 years of age (51.6%) were male; however, a majority of patients with severe GI disease (52.4%) were female.

The disease characteristics were similar among the five subgroups, with an average of 7.7-10.6 years of T2DM duration and 6.9-9.3 years of T2DM treatment duration. There was no considerable difference in the average weekly dose of dulaglutide among all the subgroups of interest, and overall the study population (1.0-1.3 mg/week).

Table 10.2.2-4 Description of dulaglutide initiators per subgroup in Sweden

	Sweden All patients (N=5,456)	Severe renal failure (N=27)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
Age (range)*						
0-4 years	none	none	none	none	none	none
5-9 years	none	none	none	none	none	none
10-14 years	none	none	none	none	none	none
15-17 years	PPD	none	none	none	none	none
18-44 years	PPD	none	PPD	PPD	22 (4.7%)	none
45-64 years	2,852 (52.3%)	PPD	114 (29.1%)	60 (58.3%)	196 (41.6%)	none
65-74 years	1,588 (29.1%)	14 (51.9%)	174 (44.4%)	28 (27.2%)	165 (35%)	none
≥ 75 years	529 (9.7%)	PPD	PPD	PPD	88 (18.7%)	529 (100%)
Mean (SD)	60.2 (11.7)	67 (9.6)	68.1 (9.8)	57.7 (10.5)	64.2 (11.2)	78.7 (3.5)
Min-Max	16 - 95	46 - 83	31 – 95	22 – 77	19 - 90	75 - 95
Median [Q1-Q3]	61 [53 - 69]	69 [63 - 72]	69 [62 - 74]	58 [51 - 66]	65 [58 - 72]	78 [76 - 80]
Children and adolescents*	PPD	none	none	none	none	none
Severe renal failure*	27 (0.5%)	27 (100%)	PPD	PPD	PPD	PPD
Hepatic disease*	103 (1.9%)	PPD	PPD	103 (100%)	PPD	PPD
Severe GI disease*	471 (8.6%)	PPD	53 (13.5%)	PPD	471 (100%)	88 (16.6%)
Heart failure*	392 (7.2%)	PPD	392 (100%)	14 (13.6%)	53 (11.3%)	97 (18.3%)
Pregnant women*	PPD	none	none	none	none	none
Breast-feeding women*	none	none	none	none	none	none
Gender						
Male	3,234 (59.3%)	15 (55.6%)	264 (67.3%)	63 (61.2%)	224 (47.6%)	273 (51.6%)
Female	2,222 (40.7%)	12 (44.4%)	128 (32.7%)	40 (38.8%)	247 (52.4%)	256 (48.4%)
T2DM duration: time since diagnosis						

	Sweden All patients (N=5,456)	Severe renal failure (N=27)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
N	5,373	25	387	102	464	521
≤ 1 year	310 (5.8%)	PPD	18 (4.7%)	PPD	23 (5%)	21 (4%)
1 – 5 years	1,166 (21.7%)	PPD	49 (12.7%)	30 (29.4%)	86 (18.5%)	49 (9.4%)
6 – 10 years	1,656 (30.8%)	PPD	91 (23.5%)	PPD	149 (32.1%)	120 (23%)
>10 years	2,241 (41.7%)	17 (68%)	229 (59.2%)	41 (40.2%)	206 (44.4%)	331 (63.5%)
Mean (SD)	8.2 (4.5)	10.6 (4.9)	10 (4.5)	7.7 (4.9)	8.7 (4.6)	10.2 (4.1)
Min-Max	0 - 20.7	0.8 - 19.5	0 - 20.6	0 - 17.3	0 - 20.4	0 - 20.6
Median [Q1-Q3]	8.6 [4.6 - 11.4]	11.8 [5.1 - 12.4]	10.9 [6.9 - 12.8]	7.6 [3 - 11.6]	8.7 [5.2 - 12]	11 [7.8 - 12.3]
Missing	83 (1.5%)	2 (7.4%)	5 (1.3%)	1 (0.9%)	7 (1.5%)	8 (1.5%)
Duration of T2DM treatment						
N	5,348	25	379	101	461	512
≤ 1 year	307 (5.7%)	PPD	15 (4%)	PPD	23 (5%)	16 (3.1%)
1 - 5 years	1,218 (22.8%)	PPD	58 (15.3%)	PPD	95 (20.6%)	53 (10.4%)
> 5 years	3,823 (71.5%)	19 (76%)	306 (80.7%)	64 (63.4%)	343 (74.4%)	443 (86.5%)
Mean (SD)	7.6 (3.7)	9.1 (3.7)	8.7 (3.5)	6.9 (4.1)	7.8 (3.7)	9.3 (3.2)
Min-Max	0 - 12.5	0.8 - 12.4	0 - 12.5	0 - 12.5	0 - 12.4	0 - 12.5
Median [Q1-Q3]	8.4 [4.5 - 10.9]	10.7 [5 - 11.8]	10.3 [6.4 - 11.4]	7.2 [2.9 - 11]	847 [4.9 - 11.1]	10.6 [7.6 - 11.6]
Missing	108 (2%)	2 (7.4%)	13 (3.3%)	2 (1.9%)	10 (2.1%)	17 (3.2%)
Dulaglutide average weekly dose (mg/week)*						
N	4,828	24	348	90	409	453
Mean (SD)	1.3 (0.3)	1 (0.3)	1.3 (0.4)	1.3 (0.3)	1.2 (0.3)	1.1 (0.4)
Min-Max	0.1 - 4.6	0.8 - 1.5	0.5 - 4.6	0.4 - 1.5	0.8 - 1.5	0.4 - 1.5
Median [Q1-Q3]	1.5 [1.2 - 1.5]	0.8 [0.8 - 1.4]	1.5 [0.8 - 1.5]	1.5 [1.3 - 1.5]	1.5 [0.8 - 1.5]	1.1 [0.8 - 1.5]
Missing	628 (11.5%)	3 (11.1%)	44 (11.2%)	13 (12.6%)	62 (13.2%)	76 (14.4%)

* Derived variable

GI: gastrointestinal; SD: standard deviation; T2DM: type 2 diabetes mellitus;
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Sweden, Table T_06

10.2.2.1.5. UK

In the UK, a total of 1,304 patients with T2DM started treatment with dulaglutide. The details of the overall population in the UK are presented in Table 10.2.2-5. Overall, a majority of the patients were within 45-64 years of age (61.0%) with a similar trend observed among patients with histories of hepatic disease (72.0%) or severe GI disease (56.0%), whereas patients with pre-existing heart failure were within 45-64 years and 65-74 years of age (40.5% each). The mean age among the overall patient population (57.4 years) was lower in comparison to subgroup patient populations. Mean age was highest in patients with a history of heart failure (66.1 years), followed by those with histories of severe GI disease (60.2%) and hepatic disease (56.3%). The gender distribution was comparable among all dulaglutide initiators in the UK, with a higher proportion of male patients across the study subgroups.

The disease characteristics were comparable among the four subgroups, with duration of disease at an average of 11.2-13.8 years since T2DM diagnosis and 8.8-10.7 years of T2DM treatment duration, which was higher than that among the overall population (time since T2DM diagnosis: 10.4 years; T2DM treatment duration: 8.7 years). There was no considerable difference in the average weekly dose of dulaglutide among all the subgroups of interest, and the overall study population (1.2-1.4 mg/week).

Table 10.2.2-5 Description of dulaglutide initiators per subgroup in UK

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
Age (range)*					
0-4 years	none	none	none	none	none
5-9 years	none	none	none	none	none
10-14 years	none	none	none	none	none
15-17 years	none	none	none	none	none
18-44 years	146 (11.2%)	none	PPD	18 (7.7%)	none
45-64 years	795 (61%)	17 (40.5%)	72 (72%)	131 (56%)	none
65-74 years	302 (23.2%)	PPD	13 (13%)	67 (28.6%)	none
≥ 75 years	61 (4.7%)	PPD	PPD	18 (7.7%)	61 (100%)
Mean (SD)	57.4 (11)	66.1 (10.9)	56.3 (10.1)	60.2 (10.8)	79 (3.7)
Min-Max	20 – 92	45 - 92	24 - 83	25 - 86	75 - 92
Median [Q1-Q3]	58 [50 - 65]	67 [60 - 72]	56 [51 - 63]	60 [54 - 67]	78 [76 - 81]
Children and adolescents*	none	none	none	none	none

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
Height (cm)					
N	669	16	52	127	26
Mean (SD)	168.7 (10.2)	168.4 (11.4)	168.8 (10.1)	166.9 (10.4)	164.4 (9.8)
Min-Max	137 – 197	152 - 183	147 - 185	137 - 190	144 - 183
Median [Q1-Q3]	169 [160 - 177]	168 [157 - 179]	168.8 [161 - 178]	165.1 [160 - 174]	163.5 [158 - 172]
Missing	635 (48.7%)	26 (61.9%)	48 (48.0%)	107 (45.7%)	35 (57.4%)
Weight (kg)					
N	1,174	33	93	218	52
Mean (SD)	105.9 (22.8)	107.5 (20.5)	102.6 (20.4)	104. (21.24)	90.6 (14.9)
Min-Max	41.4 - 198	69 - 150	57.6 - 162.4	52 - 163.7	53 - 131
Median [Q1-Q3]	104 [90 - 119]	103.4 [96 - 120]	102 [88.9 - 116]	103.6 [89 - 117]	95 [80 - 100]
Missing	130 (10%)	9 (21.4%)	7 (7%)	16 (6.8%)	9 (14.8%)
Severe renal failure*	PPD				
Hepatic disease*	100 (7.7%)	PPD	100 (100%)	26 (11.1%)	PPD
Severe GI disease*	234 (17.9%)	12 (28.6%)	26 (26%)	234 (100%)	18 (29.5%)
Heart failure*	42 (3.2%)	42 (100%)	PPD	PPD	PPD
Pregnant women*	PPD	none	none	none	none
Breast-feeding women*	none	none	none	none	none
Gender					
Male	691 (53%)	26 (61.9%)	51 (51%)	120 (51.3%)	32 (52.5%)
Female	613 (47%)	16 (38.1%)	49 (49%)	114 (48.7%)	29 (47.5%)
T2DM duration: time since diagnosis					
N	1,304	42	100	234	61
≤ 1 year	78 (6%)	PPD	PPD	PPD	PPD
1 – 5 years	180 (13.8%)	PPD	PPD	PPD	PPD
6 – 10 years	407 (31.2%)	PPD	29 (29%)	61 (26.1%)	13 (21.3%)
>10 years	639 (49%)	23 (54.8%)	57 (57%)	125 (53.4%)	41 (67.2%)
Mean (SD)	10.4 (6.4)	11.2 (6.6)	11.2 (5.4)	11.2 (6.7)	13.8 (6.9)
Min-Max	0 - 52	0.2 - 26.8	0.1 - 23.8	0 - 36.7	0 - 36.7
Median [Q1-Q3]	9.8 [6 - 14.2]	10.7 [7 - 16]	11 [7.3 - 15.2]	10.7 [6.1 - 15.4]	13.5 [9.2 - 18.4]
Duration of T2DM treatment					
N	1,304	42	100	234	61
≤ 1 year	76 (5.8%)	PPD	PPD	PPD	PPD

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
1 - 5 years	305 (23.4%)	PPD	PPD		PPD
> 5 years	923 (70.8%)	29 (69%)	72 (72%)	171 (73.1%)	49 (80.3%)
Mean (SD)	8.7 (5.4)	8.8 (6.1)	9 (5.4)	9.2 (5.5)	10.7 (5.8)
Min-Max	0 - 27.7	0.1 - 23.1	0 - 23.7	0.1 - 24.3	0.2 - 24.2
Median [Q1-Q3]	8.3 [4.5 - 12.3]	8 [3.4 - 13]	9 [4.6 - 13.4]	8.7 [4.8 - 13]	11.4 [6.4 - 14.9]
Dulaglutide average weekly dose (mg/week)*					
N	1,304	42	100	234	61
Mean (SD)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	1.2 (0.5)
Min-Max	0.2 - 3	0.6 - 2.1	0.6 - 2.3	0.3 - 2.9	0.2 - 2.3
Median [Q1-Q3]	1.5 [1 - 1.5]	1.5 [0.8 - 1.6]	1.5 [1.1 - 1.5]	1.5 [1.1 - 1.5]	1.3 [0.8 - 1.6]

* Derived variable
GI: gastrointestinal; SD: standard deviation; T2DM: type 2 diabetes mellitus;
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Sweden, Table T_06

10.2.2.2. Comorbidities and Concomitant Medications

10.2.2.2.1. France

Among the overall dulaglutide initiators from France, ischaemic heart disease, hypertension, and dyslipidemia were the most commonly reported comorbidities (Table 10.2.2-6). Dyslipidemia was more common among the subgroups than in overall dulaglutide initiators with the exception of patients with a history of heart failure. Similarly, ischaemic heart disease and hypertension were more common among the subgroups than in overall dulaglutide initiators. The same trend was visible for most comorbidities. In comparison to overall dulaglutide initiators (77.7%), the proportion of patients who were prescribed concomitant ADMs in prior 6 months was higher among the subgroups including all patients with pre-existing heart failure and 91.2% and 85% with severe GI disease and elderly patients (≥75 years), respectively. The most common ADMs at index date and at prior 6 months were biguanides, sulfonylureas, and insulins. Overall, 5% of dulaglutide initiators in France were prescribed dulaglutide in >1 weekly dose, and was relatively small across subgroups of interest.

Table 10.2.2-6 Description of comorbidities and co-medications among dulaglutide initiators per subgroup in France

	France All patients (N=1,384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
Hypertension*	1,102 (79.6%)	19 (90.5%)	60 (88.2%)	125 (94%)
Dyslipidaemia*	1,011 (73%)	15 (71.4%)	59 (86.8%)	110 (82.7%)

	France All patients (N=1,384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
Macrovascular complications*	1,110 (80.2%)	20 (95.2%)	60 (88.2%)	125 (94%)
Ischaemic heart disease*	1,110 (80.2%)	none	60 (88.2%)	125 (94%)
Stroke*	PPD	none	PPD	none
Peripheral arterial obstructive disease*	PPD			
Microvascular complications*	53 (3.8%)	none	PPD	
Diabetic neuropathy*	42 (3.0%)	none	PPD	
Diabetic retinopathy*	PPD	none	none	PPD
Diabetic nephropathy*	PPD	none	none	PPD
Solid tumours*	PPD			
Endometrium*	PPD	none	none	none
Colon*	PPD	none	PPD	
Breast*	PPD			none
Concomitant ADM during 6-month baseline*	1,075 (77.7%)	21 (100%)	62 (91.2%)	113 (85%)
Insulins *	232 (16.8%)	PPD	13 (19.1%)	27 (20.3%)
Biguanides*	726 (52.5%)	13 (61.9%)	37 (54.4%)	50 (37.6%)
Sulfonylureas / Sulfonamides*,[1]	580 (41.9%)	PPD	39 (57.4%)	56 (42.1%)
Alpha-glucosidase inhibitors*	25 (1.8%)	PPD		
Dipeptidyl peptidase-4 inhibitors*	168 (12.1%)	none	13 (19.1%)	24 (18%)
GLP-1 RAs (other than dulaglutide)*	258 (18.6%)	PPD	14 (20.6%)	24 (18%)
Meglitinides*	177 (12.8%)	PPD		30 (22.6%)
Single pill combinations of oral ADM*	325 (23.5%)	PPD	14 (20.6%)	34 (25.6%)
Concomitant ADM at index date*	1,307 (94.4%)	21 (100%)	65 (95.6%)	128 (96.2%)
Insulins *	291 (21%)	PPD	12 (17.6%)	25 (18.8%)
Biguanides*	1,057 (76.4%)	none	49 (72.1%)	77 (57.9%)
Sulfonylureas / Sulfonamides*,[1]	701 (50.7%)	PPD	40 (58.8%)	59 (44.4%)
Alpha-glucosidase inhibitors*	22 (1.6%)	none	PPD	
Dipeptidyl peptidase-4 inhibitors*	124 (9%)	PPD	12 (17.6%)	17 (12.8%)
GLP-1 RAs (other than dulaglutide)*	137 (9.9%)	PPD		16 (12%)
Meglitinides*	197 (14.2%)	PPD		35 (26.3%)
Single pill combinations of oral ADM*	245 (17.7%)	PPD		28 (21.1%)
Medication error‡	49 (5%)	PPD		PPD

* Derived variable
‡ Patients with dulaglutide prescribed >1 dose per week are considered as medication errors.
ADM: anti-diabetes medication; GI: gastrointestinal; GLP-1 RA: glucagon-like peptide 1 receptor agonist; SD: standard deviation; T2DM: type 2 diabetes mellitus
Subgroup of patients with hepatic disease has not been presented due to privacy morns (i.e. N<10)
[1]ATC codes A10BB (Sulfonylureas) and A10BC (Sulfonamides [heterocyclic]) have been placed under Sulfonylureas/Sulfonamides
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset France, Table T_06

10.2.2.2.2. Germany

Among the overall dulaglutide initiators from Germany, ischaemic heart disease, hypertension, and dyslipidaemia were the most commonly reported comorbidities (Table 10.2.2-7). Across the subgroups, hypertension was common, but proportionally lower when compared to overall dulaglutide initiators, with the exception of patients with severe GI disease. In contrast, both ischaemic heart disease and dyslipidemia were more common among the subgroups than in overall dulaglutide initiators. The same trend was visible for most comorbidities. Solid tumours were reported among subgroups of patients and ranged from 4.4% in patients with a history of heart failure to 10.6% in patients with a history of severe GI disease. Concomitant ADMs in prior 6 months were reported in a majority of patients in all subgroups (84.1% to 92.3%) and the proportions of patients were higher than that of the overall population (82.8%). The most common ADMs at the index date of dulaglutide initiation and at prior 6 months were insulins, biguanides and sodium glucose cotransporter-2 inhibitors. Dulaglutide initiators in Germany were prescribed their medication in once weekly doses.

Table 10.2.2-7 Description of comorbidities and co-medications among dulaglutide initiators per subgroup in Germany

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Hypertension*	2,875 (60.4%)	13 (50%)	202 (40.2%)	83 (55%)	239 (61.9%)	249 (51.4%)
Dyslipidaemia*	2,852 (59.9%)	21 (80.8%)	408 (81.1%)	113 (74.8%)	276 (71.5%)	346 (71.5%)
Macrovascular complications*	3,209 (67.4%)	21 (80.8%)	469 (93.2%)	119 (78.8%)	353 (91.5%)	398 (82.2%)
Ischaemic heart disease*	3,091 (65%)	20 (76.9%)	457 (90.9%)	116 (76.8%)	348 (90.2%)	382 (78.9%)
Stroke*	176 (3.7%)	PPD	41 (8.2%)	PPD	26 (6.7%)	32 (6.6%)
Peripheral arterial obstructive disease*	452 (9.5%)	PPD	94 (18.7%)	PPD	47 (12.2%)	95 (19.6%)
Microvascular complications*	2,206 (46.4%)	20 (76.9%)	325 (64.6%)	78 (51.7%)	206 (53.4%)	314 (64.9%)

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Diabetic neuropathy*	1,754 (36.9%)	17 (65.4%)	276 (54.9%)	57 (37.7%)	166 (43%)	276 (57%)
Diabetic retinopathy*	447 (9.4%)	PPD	65 (12.9%)	17 (11.3%)	45 (11.7%)	63 (13%)
Diabetic nephropathy*	814 (17.1%)	14 (53.8%)	140 (27.8%)	35 (23.2%)	94 (24.4%)	132 (27.3%)
Solid tumours*	97 (2%)	PPD	22 (4.4%)	PPD	41 (10.6%)	23 (4.8%)
Pancreas*	PPD	none	PPD	none	PPD	PPD
Endometrium*	PPD	none	PPD			
Colon*	22 (0.5%)	PPD			22 (5.7%)	PPD
Rectum*	PPD					
Breast*	44 (0.9%)	none	PPD			
Bladder*	14 (0.3%)	none	PPD	none	PPD	
Concomitant ADM during 6-month baseline*	3,939 (82.8%)	24 (92.3%)	442 (87.9%)	130 (86.1%)	331 (85.8%)	407 (84.1%)
Insulins *	2,502 (52.6%)	18 (69.2%)	326 (64.8%)	90 (59.6%)	185 (47.9%)	289 (59.7%)
Biguanides*	1,769 (37.2%)	PPD	183 (36.4%)	65 (43%)	151 (39.1%)	127 (26.2%)
Sulfonylureas / Sulfonamides*,[1]	246 (5.2%)	none	29 (5.8%)	7 (4.6%)	25 (6.5%)	23 (4.8%)
Alpha-glucosidase inhibitors*	21 (0.4%)	PPD	PPD			
Thiazolidinediones*	21 (0.4%)	none	PPD			
Dipeptidyl peptidase-4 inhibitors*	599 (12.6%)	PPD	83 (16.5%)	21 (13.9%)	78 (20.2%)	99 (20.5%)
Sodium glucose cotransporter-2 inhibitors*	837 (17.6%)	PPD	92 (18.3%)	26 (17.2%)	88 (22.8%)	75 (15.5%)
GLP-1 RAs (other than dulaglutide)*	620 (13%)	PPD	64 (12.7%)	25 (16.6%)	50 (13%)	48 (9.9%)
Meglitinides*	79 (1.7%)	PPD	PPD			
Single pill combinations of oral ADM*	751 (15.8%)	PPD	60 (11.9%)	19 (12.6%)	62 (16.1%)	49 (10.1%)

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Single injection combination of insulin and GLP-1 RA*	165 (3.5%)	none	19 (3.8%)	PPD	12 (3.1%)	21 (4.3%)
Concomitant ADM at index date*	2,242 (47.1%)	PPD	212 (42.1%)	67 (44.4%)	146 (37.8%)	180 (37.2%)
Insulins *	1,321 (27.8%)	PPD	143 (28.4%)	37 (24.5%)	87 (22.5%)	121 (25%)
Biguanides*	1,026 (21.6%)	PPD	69 (13.7%)	33 (21.9%)	54 (14%)	51 (10.5%)
Sulfonylureas / Sulfonamides*,[1]	59 (1.2%)	none	PPD			
Alpha-glucosidase inhibitors*	PPD	none	none	none	PPD	none
Thiazolidinediones*	5 (0.1%)	none	none	none	PPD	
Dipeptidyl peptidase-4 inhibitors*	77 (1.6%)	none	PPD		12 (3.1%)	12 (2.5%)
Sodium glucose cotransporter-2 inhibitors*	258 (5.4%)	PPD	22 (4.4%)	PPD	17 (4.4%)	PPD
GLP-1 RAs (other than dulaglutide)*	17 (0.4%)	none	PPD			
Meglitinides*	15 (0.3%)	none	PPD	none	none	none
Single pill combinations of oral ADM*	97 (2%)	none	15 (3%)	PPD		
Single injection combination of insulin and GLP-1 RA*	PPD	none	none	none	none	PPD
Medication error‡	none	none	none	none	none	none

* Derived variable
‡ Patients with dulaglutide prescribed >1 dose per week are considered as medication errors.
ADM: anti-diabetes medication; GI: gastrointestinal; GLP-1 RA: glucagon-like peptide 1 receptor agonist; SD: standard deviation; T2DM: type 2 diabetes mellitus
[1]ATC codes A10BB (Sulfonylureas) and A10BC (Sulfonamides [heterocyclic]) have been placed under Sulfonylureas/Sulfonamides
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Germany, Table T_06

10.2.2.2.3. Spain

Among the overall dulaglutide initiators from Spain, hypertension and dyslipidaemia were the most commonly reported comorbidities (Table 10.2.2-8). In comparison to subgroup populations, hypertension and dyslipidaemia were less common among overall dulaglutide initiators with a similar trend observed for most comorbidities. The proportion of patients who were prescribed concomitant ADMs in prior 6 months was higher among the subgroups when compared to the overall population with the exception of patients with a history of heart failure. The most common ADMs at the index date of dulaglutide initiation and at prior 6 months were insulins, biguanides, and sulfonylureas. Dulaglutide initiators in Spain were prescribed their medication in once weekly doses.

Table 10.2.2-8 Description of comorbidities and co-medications among dulaglutide initiators per subgroup in Spain

	Spain All patients (N=2,716)	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
Hypertension*	1,972 (72.6%)	34 (94.4%)	145 (81.5%)	354 (78.5%)	229 (79.8%)	195 (91.5%)
Dyslipidaemia*	1,643 (60.5%)	26 (72.2%)	116 (65.2%)	306 (67.8%)	204 (71.1%)	138 (64.8%)
Macrovascular complications*	508 (18.7%)	20 (55.6%)	77 (43.3%)	79 (17.5%)	73 (25.4%)	54 (25.4%)
Ischaemic heart disease*	354 (13%)	15 (41.7%)	60 (33.7%)	52 (11.5%)	48 (16.7%)	40 (18.8%)
Stroke*	70 (2.6%)	PPD	13 (7.3%)	14 (3.1%)	12 (4.2%)	PPD
Peripheral arterial obstructive disease*	148 (5.4%)	PPD	19 (10.7%)	23 (5.1%)	21 (7.3%)	12 (5.6%)
Microvascular complications*	529 (19.5%)	16 (44.4%)	48 (27%)	73 (16.2%)	58 (20.2%)	44 (20.7%)
Diabetic neuropathy*	PPD					-
Diabetic retinopathy*	443 (16.3%)	PPD	39 (21.9%)	55 (12.2%)	45 (15.7%)	35 (16.4%)
Diabetic nephropathy*	137 (5%)	12 (33.3%)	15 (8.4%)	26 (5.8%)	20 (7%)	14 (6.6%)
Solid tumours*	93 (3.4%)	PPD		15 (3.3%)	29 (10.1%)	PPD
Pancreas*	PPD	none	none	none	PPD	none
Endometrium*	12 (0.4%)	none	PPD	none	PPD	
Colon*	17 (0.6%)	PPD		PPD	16 (5.6%)	PPD
Rectum*	PPD	none	none	PPD	PPD	none
Breast*	38 (1.4%)	PPD				
Bladder*	25 (0.9%)	none	PPD			

	Spain All patients (N=2,716)	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
Concomitant ADM during 6-month baseline*	2,306 (84.9%)	31 (86.1%)	147 (82.6%)	388 (86%)	250 (87.1%)	187 (87.8%)
Insulins *	943 (34.7%)	18 (50%)	77 (43.3%)	161 (35.7%)	116 (40.4%)	87 (40.8%)
Biguanides*	850 (31.3%)	PPD	46 (25.8%)	138 (30.6%)	85 (29.6%)	39 (18.3%)
Sulfonylureas / Sulfonamides*,[1]	505 (18.6%)	PPD	28 (15.7%)	99 (22%)	43 (15%)	32 (15%)
Alpha-glucosidase inhibitors*	PPD	none	none	none	1 (0.3%)	none
Thiazolidinediones*	42 (1.5%)	PPD				
Dipeptidyl peptidase-4 inhibitors*	291 (10.7%)	PPD	16 (9%)	52 (11.5%)	38 (13.2%)	37 (17.4%)
Sodium glucose cotransporter-2 inhibitors*	290 (10.7%)	PPD	12 (6.7%)	57 (12.6%)	25 (8.7%)	21 (9.9%)
GLP-1 RAs (other than dulaglutide)*	450 (16.6%)	PPD	24 (13.5%)	81 (18%)	56 (19.5%)	29 (13.6%)
Meglitinides*	152 (5.6%)	PPD	12 (6.7%)	19 (4.2%)	18 (6.3%)	24 (11.3%)
Single pill combinations of oral ADM*	821 (30.2%)	PPD	44 (24.7%)	124 (27.5%)	75 (26.1%)	63 (29.6%)
Concomitant ADM at index date*	2,058 (75.8%)	30 (83.3%)	131 (73.6%)	341 (75.6%)	219 (76.3%)	156 (73.2%)
Insulins *	878 (32.3%)	16 (44.4%)	70 (39.3%)	152 (33.7%)	105 (36.6%)	74 (34.7%)
Biguanides*	1,073 (39.5%)	PPD	51 (28.7%)	164 (36.4%)	94 (32.8%)	68 (31.9%)
Sulfonylureas / Sulfonamides*,[1]	298 (11%)	PPD	19 (10.7%)	62 (13.7%)	27 (9.4%)	18 (8.5%)
Thiazolidinediones*	31 (1.1%)	PPD	PPD			
Dipeptidyl peptidase-4 inhibitors*	93 (3.4%)	PPD		15 (3.3%)	14 (4.9%)	20 (9.4%)
Sodium glucose cotransporter-2 inhibitors*	92 (3.4%)	PPD		15 (3.3%)	PPD	
GLP-1 RAs (other than dulaglutide)*	27 (1%)	none	PPD			
Meglitinides*	83 (3.1%)	PPD				16 (7.5%)
Single pill combinations of oral ADM*	373 (13.7%)	PPD	21 (11.8%)	66 (14.6%)	39 (13.6%)	20 (9.4%)
Medication error‡	none	none	none	none	none	none

* Derived variable
‡ Patients with dulaglutide prescribed >1 dose per week are considered as medication errors.
ADM: anti-diabetes medication; GI: gastrointestinal; GLP-1 RA: glucagon-like peptide 1 receptor agonist; SD: standard deviation; T2DM: type 2 diabetes mellitus
[1]ATC codes A10BB (Sulfonylureas) and A10BC (Sulfonamides [heterocyclic]) have been placed under Sulfonylureas/Sulfonamides
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Spain, Table T_06

10.2.2.2.4. Sweden

Among the overall dulaglutide initiators from Sweden; hypertension, ischaemic heart disease and dyslipidaemia were the most commonly reported comorbidities (Table 10.2.2-9). Dyslipidemia and ischaemic heart disease were more common among the subgroups than in overall dulaglutide initiators with the exception of patients with a history of heart failure. Similarly, hypertension was more common among the subgroups than in overall dulaglutide initiators. The same trend was visible for most comorbidities. Solid tumours were less frequent among subgroups of dulaglutide initiators and ranged from none in patients with a history of severe renal failure to 3.2% in those ≥75 years of age. Concomitant ADMs during 6 months baseline period were reported in the majority of dulaglutide initiators in all subgroups (88.9% to 97.2%) and was comparable to that in the overall population. The most common ADMs at index date of starting dulaglutide therapy and prior to 6 months were biguanides, insulins, and dipeptidyl peptidase-4 inhibitors. Overall, 10 patients started dulaglutide in >1 weekly dose, including one patient with a history of heart failure and two patients ≥75 years of age.

Table 10.2.2-9 Description of comorbidities and co-medications among dulaglutide initiators per subgroup in Sweden

	Sweden All patients (N=5,456)	Severe renal failure (N=27)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
Hypertension*	4,636 (85%)	27 (100%)	392 (100%)	88 (85.4%)	424 (90%)	517 (97.7%)
Dyslipidaemia*	4,447 (81.5%)	24 (88.9%)	363 (92.6%)	63 (61.2%)	393 (83.4%)	473 (89.4%)
Macrovascular complications*	4,542 (83.2%)	27 (100%)	391 (99.7%)	82 (79.6%)	422 (89.6%)	515 (97.4%)
Ischaemic heart disease*	4523 (82.9%)	27 (100%)	391 (99.7%)	82 (79.6%)	421 (89.4%)	514 (97.2%)
Stroke*	306 (5.6%)	PPD	58 (14.8%)	PPD	36 (7.6%)	77 (14.6%)
Peripheral arterial obstructive disease*	148 (2.7%)	PPD	34 (8.7%)	PPD	14 (3%)	37 (7%)
Microvascular complications*	1,260 (23.1%)	17 (63%)	139 (35.5%)	28 (27.2%)	109 (23.1%)	167 (31.6%)
Diabetic neuropathy*	250 (4.6%)	PPD	41 (10.5%)	PPD	38 (8.1%)	28 (5.3%)

	Sweden All patients (N=5,456)	Severe renal failure (N=27)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
Diabetic retinopathy*	1,080 (19.8%)	13 (48.1%)	120 (30.6%)	22 (21.4%)	84 (17.8%)	148 (28%)
Diabetic nephropathy*	188 (3.4%)	13 (48.1%)	30 (7.7%)	5 (4.9%)	20 (4.2%)	19 (3.6%)
Solid tumours*	107 (2%)	none	PPD		14 (3%)	17 (3.2%)
Liver*	PPD	none	none	PPD	none	PPD
Pancreas*	PPD	none	none	none	1 (0.2%)	PPD
Endometrium*	PPD	none	none	none	none	none
Colon*	27 (0.5%)	none	PPD	none	PPD	PPD
Rectum*	PPD	none	PPD	none	PPD	PPD
Breast*	41 (0.8%)	none	PPD	PPD	PPD	PPD
Bladder*	24 (0.4%)	none	PPD	PPD	PPD	PPD
Concomitant ADM during 6-month baseline*	5,299 (97.1%)	24 (88.9%)	381 (97.2%)	99 (96.1%)	457 (97%)	508 (96%)
Insulins *	2,408 (44.1%)	18 (66.7%)	244 (62.2%)	55 (53.4%)	251 (53.3%)	292 (55.2%)
Biguanides*	4,113 (75.4%)	PPD	232 (59.2%)	70 (68%)	317 (67.3%)	309 (58.4%)
Sulfonylureas / Sulfonamides*,[1]	971 (17.8%)	PPD	65 (16.6%)	13 (12.6%)	73 (15.5%)	114 (21.6%)
Alpha-glucosidase inhibitors*	29 (0.5%)	none	PPD	none	PPD	
Thiazolidinediones*	150 (2.7%)	none	PPD		13 (2.8%)	13 (2.5%)
Dipeptidyl peptidase-4 inhibitors*	1,510 (27.7%)	11 (40.7%)	104 (26.5%)	20 (19.4%)	143 (30.4%)	179 (33.8%)
Sodium glucose cotransporter-2 inhibitors*	976 (17.9%)	PPD	76 (19.4%)	17 (16.5%)	86 (18.3%)	59 (11.2%)
GLP-1 RAs (other than dulaglutide)*	999 (18.3%)	PPD	64 (16.3%)	22 (21.4%)	72 (15.3%)	70 (13.2%)
Meglitinides*	239 (4.4%)	PPD	15 (3.8%)	PPD	23 (4.9%)	17 (3.2%)
Single pill combinations of oral ADM*	321 (5.9%)	none	17 (4.3%)	PPD	22 (4.7%)	17 (3.2%)
Single injection combination of insulin and GLP-1 RA*	33 (0.6%)	none	PPD	none	PPD	
Concomitant ADM at index date*	5,003 (91.7%)	23 (85.2%)	360 (91.8%)	88 (85.4%)	438 (93%)	473 (89.4%)

	Sweden All patients (N=5,456)	Severe renal failure (N=27)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
Insulins *	2,182 (40%)	15 (55.6%)	224 (57.1%)	50 (48.5%)	222 (47.1%)	262 (49.5%)
Biguanides*	3,351 (61.4%)	PPD	187 (47.7%)	56 (54.4%)	257 (54.6%)	245 (46.3%)
Sulfonylureas / Sulfonamides*,[1]	724 (13.3%)	PPD	44 (11.2%)	PPD	50 (10.6%)	74 (14%)
Alpha-glucosidase inhibitors*	20 (0.4%)	none	PPD	none	PPD	PPD
Thiazolidinediones*	127 (2.3%)	none	PPD			12 (2.3%)
Dipeptidyl peptidase-4 inhibitors*	1,100 (20.2%)	PPD	79 (20.2%)	12 (11.7%)	110 (23.4%)	138 (26.1%)
Sodium glucose cotransporter-2 inhibitors*	768 (14.1%)	PPD	61 (15.6%)	14 (13.6%)	73 (15.5%)	54 (10.2%)
GLP-1 RAs (other than dulaglutide)*	741 (13.6%)	PPD	51 (13%)	15 (14.6%)	57 (12.1%)	53 (10%)
Meglitinides*	194 (3.6%)	PPD			19 (4%)	15 (2.8%)
Single pill combinations of oral ADM*	238 (4.4%)	none	PPD		12 (2.5%)	12 (2.3%)
Single injection combination of insulin and GLP-1 RA*	28 (0.5%)	none	PPD	none	PPD	
Medication error‡	PPD	none	PPD	none	none	PPD

* Derived variable
‡ Patients with dulaglutide prescribed >1 dose per week are considered as medication errors.
ADM: anti-diabetes medication; GI: gastrointestinal; GLP-1 RA: glucagon-like peptide 1 receptor agonist; SD: standard deviation; T2DM: type 2 diabetes mellitus
[1]ATC codes A10BB (Sulfonylureas) and A10BC (Sulfonamides [heterocyclic]) have been placed under Sulfonylureas/Sulfonamides
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Sweden, Table T_06

10.2.2.2.5. UK

Among the overall dulaglutide initiators from the UK; ischaemic heart disease, hypertension, diabetic retinopathy and dyslipidaemia were the most commonly reported comorbidities (Table 10.2.2-10). The proportion of patients with diabetic retinopathy was comparable across all subgroups. Hypertension and ischaemic heart disease were more common among the subgroups than in overall dulaglutide initiators with the exception of patients with a history of hepatic disease. Similarly, hypertension was more common among the subgroups than in overall dulaglutide initiators. The presence of comorbidities varied between overall dulaglutide initiators and among the subgroups. Solid tumours were less frequent among subgroups of dulaglutide initiators and ranged from 1% in patients with a history of hepatic disease to 2.4% in those with a

history of heart failure. Concomitant ADMs during 6 months baseline period were reported in the majority of patients in all subgroups (77% to 85.5%) but the proportion was lower in comparison to overall dulaglutide initiators. The most common ADMs at the index date of dulaglutide initiation and at prior 6 months were biguanides, sulfonylureas/sulfonamides, and sodium glucose cotransporter-2 inhibitors. Overall, a majority of patients started dulaglutide in >1 weekly dose (84.3%) and was higher than that reported across subgroups, which ranged from 75.4% to 82.5%.

Table 10.2.2-10 Description of comorbidities and co-medications among dulaglutide initiators per subgroup in UK

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
Hypertension*	776 (59.5%)	31 (73.8%)	58 (58%)	154 (65.8%)	46 (75.4%)
Dyslipidaemia*	397 (30.4%)	16 (38.1%)	41 (41%)	87 (37.2%)	27 (44.3%)
Macrovascular complications*	1,052 (80.7%)	41 (97.6%)	80 (80%)	202 (86.3%)	58 (95.1%)
Ischaemic heart disease*	1,051 (80.6%)	41 (97.6%)	80 (80%)	201 (85.9%)	58 (95.1%)
Stroke*	26 (2%)	none	PPD		
Peripheral arterial obstructive disease*	24 (1.8%)	PPD			
Microvascular complications*	462 (35.4%)	15 (35.7%)	37 (37%)	88 (37.6%)	28 (45.9%)
Diabetic neuropathy*	50 (3.8%)	PPD		12 (5.1%)	PPD
Diabetic retinopathy*	438 (33.6%)	14 (33.3%)	35 (35%)	79 (33.8%)	26 (42.6%)
Diabetic nephropathy*	PPD	none	none	PPD	none
Solid tumours*	19 (1.5%)	PPD			
Pancreas*	PPD	none	none	none	none
Endometrium*	PPD	none	none	none	none
Colon*	PPD	none	none	1 (0.4%)	none
Rectum*	PPD	none	none	none	none
Breast*	PPD				none
Bladder*	PPD	none	none	PPD	
Concomitant ADM during 6-month baseline*	1,136 (87.1%)	34 (81%)	83 (83%)	200 (85.5%)	47 (77%)
Insulins *	24 (1.8%)	PPD			
Biguanides*	823 (63.1%)	26 (61.9%)	62 (62%)	139 (59.4%)	32 (52.5%)
Sulfonylureas / Sulfonamides*,[1]	441 (33.8%)	14 (33.3%)	36 (36%)	75 (32.1%)	25 (41%)
Alpha-glucosidase inhibitors*	PPD	none	PPD		none
Thiazolidinediones*	84 (6.4%)	none	PPD	14 (6%)	PPD

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
Dipeptidyl peptidase-4 inhibitors*	362 (27.8%)	PPD	17 (17%)	65 (27.8%)	21 (34.4%)
Sodium glucose cotransporter-2 inhibitors*	421 (32.3%)	PPD	31 (31%)	78 (33.3%)	PPD
GLP-1 RAs (other than dulaglutide)*	90 (6.9%)	PPD		21 (9%)	PPD
Meglitinides*	PPD	none	none	PPD	none
Single pill combinations of oral ADM*	26 (2.%)	none	PPD		none
Single injection combination of insulin and GLP-1 RA*	PPD	none	none	PPD	none
Concomitant ADM at index date*	985 (75.5%)	27 (64.3%)	68 (68%)	169 (72.2%)	38 (62.3%)
Insulins *	PPD	none	none	PPD	none
Biguanides*	686 (52.6%)	18 (42.9%)	50 (50%)	109 (46.6%)	23 (37.7%)
Sulfonylureas / Sulfonamides*,[1]	365 (28%)	PPD	30 (30%)	65 (27.8%)	21 (34.4%)
Alpha-glucosidase inhibitors*	PPD	none	none	PPD	none
Thiazolidinediones*	62 (4.8%)	none	PPD		
Dipeptidyl peptidase-4 inhibitors*	260 (19.9%)	PPD		44 (18.8%)	15 (24.6%)
Sodium glucose cotransporter-2 inhibitors*	316 (24.2%)	PPD	21 (21%)	59 (25.2%)	PPD
GLP-1 RAs (other than dulaglutide)*	12 (0.9%)	none	PPD		
Meglitinides*	PPD	none	none	none	none
Single pill combinations of oral ADM*	18 (1.4%)	none	PPD		none
Medication error‡	1,099 (84.3%)	34 (81%)	82 (82%)	193 (82.5%)	46 (75.4%)

* Derived variable
‡ Patients with dulaglutide prescribed >1 dose per week are considered as medication errors.
ADM: anti-diabetes medication; GI: gastrointestinal; GLP-1 RA: glucagon-like peptide 1 receptor agonist; SD: standard deviation; T2DM: type 2 diabetes mellitus; UK: United Kingdom
[1]ATC codes A10BB (Sulfonylureas) and A10BC (Sulfonamides [heterocyclic]) have been placed under Sulfonylureas/Sulfonamides
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset UK, Table T_06

10.2.3. Clinical laboratory tests

10.2.3.1. Overall

Clinical laboratory tests during 6 months prior to dulaglutide initiation are summarised in Table 10.2.3-1. Clinical laboratory tests were documented across all countries except Sweden, where laboratory test results were not available for this study.

Most of dulaglutide initiators reported baseline glycosylated haemoglobin (HbA1c) >7.5% across study countries, with the UK having the highest proportion of patients (89.2%) and France with the lowest proportion (60.7%). The mean HbA1c (%) was similar across Germany, Spain and the UK (9.4-9.5%) except France where the mean HbA1c (%) was 8%.

Estimated glomerular filtration rate (eGFR) value was ≥30 mL/min/1.73 m^2 in more than 94% of patients across study countries. The mean eGFR value was reported highest in Germany (131.4 mL/min/1.73 m^2), followed by France (87.0 mL/min/1.73 m^2), Spain (71.2 mL/min/1.73 m^2), and the UK (69.1 mL/min/1.73 m^2).

Serum creatinine values were <100 µmol/L in a majority of female patients (the UK: 91.6%, Germany: 88.7%, and Spain: 73.4%). The mean serum creatinine value in females was highest in Germany (74.2 µmol/L), followed by Spain (73.9 µmol/L) and the UK (71.0 µmol/L). A similar trend was observed among male patients across these countries with most of the patients having serum creatinine values of <120 µmol/L (the UK: 89.4%, Germany: 86.7%, and Spain: 70.8%) with Spain reporting the highest mean value (96.4 µmol/L), followed by Germany (93.7 µmol/L) and the UK (88.9 µmol/L). The number of patients in France with serum creatinine values was too small to evaluate.

Urine albumin/creatinine ratio (UACR) was documented only in patients from the UK and Spain with most of the patients having UACR <30 mg/g (the UK: 91.7% and Spain: 62.4%).

Most dulaglutide initiators across all countries had LDL cholesterol <1.6 g/L, with Spain having the highest proportion (89.1%), and Germany with the lowest proportion (64.4%) of patients. The mean LDL cholesterol was highest in patients from Spain (2.6 g/L), followed by patients from France, Germany, and the UK having similar mean values (1.2-1.5 g/L). HDL cholesterol value was ≥0.35 g/L in a majority of patients across all the countries with France having the highest proportion (81.9%), and Germany with the lowest proportion (62.6%) of patients. The mean HDL cholesterol was highest in patients from Spain (0.9 g/L), followed by patients from France, Germany, and the UK having similar mean values (0.4-0.5 g/L).

Across all countries, both female and male dulaglutide initiators had aspartate amino transferase (AST) values of <2*ULNR (>91%), except the UK, where 73.3% of female patients had AST

<2*ULNR. Among female patients, the mean AST was highest in Germany (37.4 IU/L), followed by Spain, the UK, and France (33.8, 29.2, and 27.2 IU/L, respectively). Among male patients, the mean AST was highest in Germany (41.3 IU/L), followed by Spain, France and the UK (35.2, 28.3, and 26.3 IU/L, respectively).

A similar trend was also observed for alanine amino transferase (ALT) test; a majority of patients across France, Spain and the UK had ALT <2*ULNR among both the genders (>91%), while in Germany, more than 84% patients reported the same. Among female patients, the mean ALT value was highest in Germany (47.4 IU/L), followed by France, Spain and the UK (36.5, 35, and 28.6 IU/L, respectively). Among male patients, the mean ALT was highest in Germany (56.9 IU/L), followed by Spain, France and the UK (41.9, 39.6, and 34.5 IU/L, respectively).

Table 10.2.3-1 Description of the clinical laboratory tests in patients started treatment with dulaglutide

	France (N=1,384)	**Germany (N=4,759)**	**Spain (N=2,716)**	**UK (N=1,304)**
Clinical laboratory tests: HbA1c (%) *				
N	178 (12.9%)	2,989 (62.8)	2,370 (87.3%)	1,193 (91.5%)
≤ 6.5%	14 (7.9%)	162 (5.4%)	99 (4.2%)	31 (2.6%)
6.6% - 7.5%	56 (31.5%)	266 (8.9%)	207 (8.7%)	98 (8.2%)
>7.5%	108 (60.7%)	2,561 (85.7%)	2,064 (87.1%)	1,064 (89.2%)
Mean (SD)	8 (1.4)	9.5 (1.9)	9.4 (1.8)	9.4 (1.7)
Min-Max	5.1 - 15.6	5 - 17.7	4.8 - 17.1	2.6 - 17.3
Median [Q1-Q3]	7.9 [7.1 - 8.6]	9.3 [8.2 - 10.7]	9.3 [8.2 - 10.5]	9.3 [8.3 - 10.5]
Missing	1,206 (87.1%)	1,770 (37.2%)	346 (12.7%)	111 (8.5%)
Clinical laboratory tests: eGFR (mL/min/1.7m^2)*				
N	103 (7.4%)	1,127 (23.7%)	1,752 (64.5%)	1,087 (83.4%)
< 30 mL/min/1.73 m^2	PPD		29 (1.7%)	58 (5.3%)
≥ 30 mL/min/1.73 m^2	101 (98.1%)	1,124 (99.7%)	1,723 (98.3%)	1,029 (94.7%)
Mean (SD)	87 (24.4)	131.4 (54.7)	71.2 (19.5)	69.2 (22.2)
Min-Max	19.2 - 160.9	12.8 - 431.0	4.4 - 132.5	0.7 - 115
Median [Q1-Q3]	88 [73 - 105]	123.7 [91.8 - 160.8]	66 [60 - 90]	72 [60 - 90]
Missing	1,281 (92.6%)	3,632 (76.3%)	964 (35.5%)	217 (16.6%)
Clinical laboratory tests: Serum creatinine (female) (µmol/L)*¶				
N	PPD	487 (22.9%)	1,224 (89.9%)	510 (83.2%)
< 100 µmol/L	-	432 (88.7%)	898 (73.4%)	467 (91.6%)
≥100 µmol/L	PPD	55 (11.3%)	326 (26.6%)	43 (8.4%)
Mean (SD)	157.4 (108.1)	74.2 (23.9)	73.9 (24.8)	71.1 (19.1)
Min-Max	103.5 - 376.1	33.6 - 185.9	0.6 - 212.2	33 - 187
Median [Q1-Q3]	108.4 [106.2 - 141.6]	69.9 [58.4 - 83.2]	70.7 [61 - 83.1]	67 [59 - 79]
Missing	622 (99%)	1,642 (77.1%)	137 (10.1%)	103 (16.8%)
Clinical laboratory tests: Serum creatinine (male) (µmol/L)* ¶				
N	(0.9%)	640 (24.3%)	1,175 (86.7%)	584 (84.5%)
< 120 µmol/L	PPD	555 (86.7%)	832 (70.8%)	522 (89.4%)
≥120 µmol/L	PPD	85 (13.3%)	343 (29.2%)	62 (10.6%)
Mean (SD)	216.7 (192.8)	93.7 (32.1)	96.4 (39.5)	88.9 (24.3)
Min-Max	115.1 - 646.1	42.5 - 539.9	0.7 - 618.1	38 - 229
Median [Q1-Q3]	153.1 [115.1 - 214.2]	88.5 [75.2 - 103.5]	88.4 [76.9 - 106.1]	84 [72.5 - 99]
Missing	749 (99.1%)	1,990 (75.7%)	180 (13.3%)	107 (15.5%)

	France (N=1,384)	Germany (N=4,759)	Spain (N=2,716)	UK (N=1,304)
Urine albumin positive*	9 (50%)	-	380 (35.8%)	11 (26.8%)
Clinical laboratory tests: UACR (mg/g)*				
N	none	none	1,907 (70.2%)	471 (36.1%)
< 30 mg/g	-	-	1,190 (62.4%)	432 (91.7%)
≥30 mg/g	-	-	717 (37.6%)	39 (8.3%)
Mean (SD)	-	-	130.1 (350.1)	25.2 (248.4)
Min-Max	-	-	0 – 2,999.2	0 – 5,247.2
Median [Q1-Q3]	-	-	16.8 [6.1 - 69.5]	0.02 [0 - 0.2]
Missing	1,384 (100%)	4,759 (100%)	809 (29.8%)	833 (63.9%)
Clinical laboratory tests: LDL cholesterol (g/L)*				
N	66 (4.8%)	3,007 (63.2%)	2,239 (82.4%)	784 (60.1%)
< 1.6 g/L	56 (84.8%)	1,938 (64.4%)	1,995 (89.1%)	658 (83.9%)
≥1.6 g/L	PPD	1,069 (35.6%)	244 (10.9%)	126 (16.1%)
Mean (SD)	1.3 (0.5)	1.5 (1.5)	2.6 (13.5)	1.2 (0.5)
Min-Max	0.9 - 5	0 - 65.3	0.2 - 185	0.2 - 5.4
Median [Q1-Q3]	1.2 [1 - 1.3]	1.4 [1.2 - 1.7]	1.1 [0.9 - 1.4]	1.1 [0.9 - 1.4]
Missing	1,318 (95.2%)	1,752 (36.8%)	477 (17.6%)	520 (39.9%)
Clinical laboratory tests: HDL cholesterol (g/L)*				
N	94 (6.8%)	3,102 (65.2%)	2,369 (87.2%)	892 (68.4%)
< 0.35 g/L	17 (18.1%)	1,160 (37.4%)	717 (30.3%)	259 (29%)
≥ 0.35 g/L	77 (81.9%)	1,942 (62.6%)	1652 (69.7%)	633 (71%)
Mean (SD)	0.5 (0.1)	0.4 (0.1)	0.9 (4.6)	0.4 (0.1)
Min-Max	0.3 - 0.7	0 - 1.0	0.1 - 64	0.2 - 1.5
Median [Q1-Q3]	0.4 [0.4 - 0.5]	0.4 [0.3 - 0.4]	0.4 [0.3 - 0.5]	0.4 [0.3 - 0.5]
Missing	1,290 (93.2%)	1,657 (34.8%)	347 (12.8%)	412 (31.6%)
Clinical laboratory tests: AST (Female) (IU/L)*				
N	38 (6.1%)	972 (45.7%)	701 (51.5%)	45 (7.3%)
< 2*ULNR	PPD	890 (91.6%)	646 (92.2%)	33 (73.3%)
≥2*ULNR	PPD	82 (8.4%)	55 (7.8%)	12 (26.7%)
Mean (SD)	27.2 (17)	37.4 (31.4)	33.8 (25.8)	29.2 (22.5)
Min-Max	10 - 86	0.2 - 392	8 - 287	10 - 118
Median [Q1-Q3]	22 [18 - 29]	29 [22 - 43.1]	25 [19 - 39]	19 [15 - 37]
Missing	590 (93.9%)	1,157 (54.3%)	660 (48.5%)	568 (92.7%)
Clinical laboratory tests: AST (Male) (IU/L)*				
N	29 (3.8%)	1,188 (45.2%)	697 (51.4%)	63 (9.1%)
< 2*ULNR	29 (100%)	1,122 (94.4%)	669 (96%)	PPD
≥2*ULNR	-	66 (5.6%)	28 (4%)	PPD
Mean (SD)	28.3 (14.8)	41.3 (44)	35.2 (21.9)	26.3 (13)
Min-Max	15 - 76	0.2 - 1065	7 - 162	7 - 74
Median [Q1-Q3]	24 [18 - 31]	32.2 [24 - 48]	28 [21 - 43]	23 [17 - 34]
Missing	727 (96.2%)	1,442 (54.8%)	658 (48.6%)	628 (90.9%)
Clinical laboratory tests: ALT (Female) (IU/L)*				
N	37 (5.9%)	1,042 (48.9%)	1,175 (86.3%)	391 (63.8%)
< 2*ULNR	PPD	884 (84.8%)	1,101 (93.7%)	377 (96.4%)
≥2*ULNR	PPD	158 (15.2%)	74 (6.3%)	14 (3.6%)
Mean (SD)	36.5 (29.1)	47.4 (39.4)	35 (27.1)	28.6 (15.6)
Min-Max	9 - 136	0.2 - 346	8 - 306	7 - 91
Median [Q1-Q3]	28 [21 - 40]	38 [24 - 57]	27 [19 - 40]	25 [17 - 35]
Missing	591 (94.1%)	1,087 (51.1%)	186 (13.7%)	222 (36.2%)
Clinical laboratory tests: ALT (Male) (IU/L)*				
N	33 (4.3%)	1,298 (49.4%)	1,129 (83.3%)	426 (61.6%)

	France (N=1,384)	Germany (N=4,759)	Spain (N=2,716)	UK (N=1,304)
< 2*ULNR	PPD	1,145 (88.2%)	1,063 (94.2%)	PPD
≥2*ULNR	PPD	153 (11.8%)	66 (5.8%)	PPD
Mean (SD)	39.6 (22.7)	56.9 (51.9)	41.9 (28.3)	34.5 (18.9)
Min-Max	15 - 103	0.2 - 728	8 - 286	5 - 125
Median [Q1-Q3]	29 [21 - 54]	45 [31 - 69]	34 [24 - 51]	30 [22 - 42]
Missing	723 (95.6%)	1,332 (50.6%)	226 (16.7%)	265 (38.4%)

* Derived variable, values measured during the baseline period closer to the index date of dulaglutide initiation.
AST: aspartate amino transferase; ALT: alanine amino transferase; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HDL: high density lipoprotein; LDL: low density lipoprotein; SD: standard deviation; UACR: urine albumin/creatinine ratio; UK: United Kingdom
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Germany, Table T_03; France, Table T_03; Spain, Table T_03, Sweden, Table T_03; UK, Table T_03

10.2.3.2. By populations of interest

10.2.3.2.1. France

Details of the overall population in France are presented in Table 10.2.3-2. More than 60% of dulaglutide initiators had a reported HbA1c >7.5% with a mean value ranging between 7.7% to 8.5 % across the study groups. An eGFR value ≥30 mL/min/1.73 m^2 was observed across the study groups with patients with a history of severe GI disease being the highest in proportion (100%), followed by patients aged ≥75 years (90.9%) and patients with pre-existing heart failure (66.7%). The mean value ranged between 59.9 and 104.8 mL/min/1.73 m^2 with the highest reported in patients with a history of severe GI disease.

PPD

Patients with heart failure PPD severe GI disease PPD, and patients aged ≥75 years PPD had LDL cholesterol <1.6 g/L with elderly patients having the highest mean LDL cholesterol (1.4 g/L). Patients with heart failure PPD severe GI disease PPD and patients aged ≥75 years PPD had HDL cholesterol ≥0.35 g/L with comparable mean HDL values across these subgroups (0.4-0.5 g/L).

AST values of <2*ULNR were reported in three women aged ≥75 years with a mean value of 22.3 IU/L. A similar trend was observed among male patients with histories of heart failure and severe GI disease (one each) with a mean value of 27.0 IU/L across the two subgroups. Similarly, ALT values of <2*ULNR were reported in six patients with pre-existing severe GI disease and PPD women aged ≥75 years with a mean value of 37.0 IU/L and 23.0 IU/L, respectively. A similar trend was observed among male patients with histories of heart failure PPD and severe GI disease PPD, and elderly patients PPD with a mean value of 23.5 IU/L, 68.0 IU/L, and 16.5 IU/L, respectively.

Table 10.2.3-2 Description of the clinical laboratory tests reported per subgroup in France

	France All patients (N=1,384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
Clinical laboratory tests: HbA1c (%) *				
N	178 (12.9%)	PPD	PPD	23 (17.3%)
≤ 6.5%	14 (7.9%)	PPD	PPD	PPD
6.6% - 7.5%	56 (31.5%)	none	PPD	PPD
>7.5%	108 (60.7%)	PPD	PPD	14 (60.9%)
Mean (SD)	8 (1.4)	8.5 (1.45)	7.7 (1)	7.8 (0.7)
Min-Max	5.1 - 15.6	6.5 - 10.3	5.5 - 9.1	6.5 - 9.4
Median [Q1-Q3]	7.9 [7.1 - 8.6]	8.6 [8.3 - 8.6]	7.9 [7.5 - 8.0]	7.7 [7.2 - 8.4]
Missing	1,206 (87.1%)	16 (76.2%)	59 (86.8%)	110 (82.7%)
Clinical laboratory tests: eGFR (mL/min/1.73 m2*)				
N	103 (7.4%)	3 (14.3%)	5 (7.4%)	PPD
< 30 mL/min/1.73 m^2	PPD		none	PPD
≥ 30 mL/min/1.73 m^2	101 (98.1%)	PPD	PPD	
Mean (SD)	87 (24.4)	68.5 (37.9)	104.8 (40.4)	59.9 (21.2)
Min-Max	19.2 - 160.9	30 - 105.7	59 - 160.9	30 - 88
Median [Q1-Q3]	88 [73 - 105]	69.9 [30 - 105]	111 [73 - 120]	66 [38.8 - 80]
Missing	1,281 (92.6%)	18 (85.7%)	63 (92.6%)	122 (91.7%)
Clinical laboratory tests: Serum creatinine (female)(µmol/L)*				
N	PPD	PPD	none	PPD
< 100 µmol/L	none	none	none	none
≥100 µmol/L	PPD	PPD	none	PPD
Mean (SD)	157.4 (108.1)	141.6 (n/a)	-	123.9 (25)
Min-Max	103.5 - 376.1	141.6 - 141.6	-	106.2 - 141.6
Median [Q1-Q3]	108.4 [106.2 - 141.6]	141.6 [141.6 - 141.6]	-	123.9 [106.2 - 141.6]
Missing	622 (99%)	6 (85.7%)	38 (100%)	69 (97.2%)
Clinical laboratory tests: Serum creatinine (male)(µmol/L)*				
N	PPD	none	none	PPD
< 120 µmol/L	PPD	none	none	none
≥120 µmol/L	PPD	none	none	PPD
Mean (SD)	216.7 (192.6)	-	-	153.1 (n/a)
Min-Max	115.1 - 646.1	-	-	153.1 - 153.1
Median [Q1-Q3]	153.1 [115.1 - 214.2]	-	-	153.1 [153.1 - 153.1]

	France All patients (N=1,384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
Missing	749 (99.1%)	14 (100%)	30 (100%)	61 (98.4%)
Urine albumin positive*	PPD	-	-	-
Clinical laboratory tests: LDL cholesterol (g/L)*				
N	66 (4.8%)	PPD	PPD	PPD
< 1.6 g/L	PPD	PPD	PPD	PPD
≥1.6 g/L	PPD	none	none	1 (33.3%)
Mean (SD)	1.3 (0.5)	0.9 (n/a)	1.1 (0.1)	1.4 (0.4)
Min-Max	0.9 - 5	0.9 - 0.9	1 - 1.3	1 - 1.8
Median [Q1-Q3]	1.2 [1 - 1.3]	0.9 [0.9 - 0.9]	1.1 [1 - 1.2]	1.3 [1 - 1.8]
Missing	1,318 (95.2%)	20 (95.2%)	63 (92.6%)	130 (97.7%)
Clinical laboratory tests: HDL cholesterol (g/L)*				
N	94 (6.8%)	PPD	PPD	PPD
< 0.35 g/L	17 (18.1%)	none	PPD	PPD
≥ 0.35 g/L	77 (81.9%)	PPD	PPD	PPD
Mean (SD)	0.5 (0.1)	0.4 (0.1)	0.4 (0.1)	0.5 (0.1)
Min-Max	0.3 - 0.7	0.4 - 0.5	0.3 - 0.5	0.3 - 0.7
Median [Q1-Q3]	0.4 [0.4 - 0.5]	0.4 [0.4 - 0.5]	0.4 [0.3 - 0.5]	0.5 [0.4 - 0.6]
Missing	1,290 (93.2%)	19 (90.5%)	62 (91.2%)	126 (94.7%)
Clinical laboratory tests: AST (Female) (IU/L)*				
N	38 (6.1%)	none	PPD	PPD
< 2*ULNR	PPD	none	PPD	PPD
≥2*ULNR	PPD	none	none	none
Mean (SD)	27.2 (17)	-	27.2 (11.3)	22.3 (6.5)
Min-Max	10 - 86	-	18 - 47	16 - 29
Median [Q1-Q3]	22 [18 - 29]	-	22.5 [19 - 34]	22 [16 - 29]
Missing	590 (93.9%)	7 (100%)	32 (84.2%)	68 (95.8%)
Clinical laboratory tests: AST (Male) (IU/L)*				
N	29 (3.8%)	PPD	PPD	none
< 2*ULNR	29 (100%)	PPD	PPD	none
≥2*ULNR	none	none	none	none
Mean (SD)	28.3 (14.8)	27 (n/a)	27 (n/a)	-
Min-Max	15 - 76	27 - 27	27 - 27	-
Median [Q1-Q3]	24 [18 - 31]	27 [27 - 27]	27 [27 - 27]	-
Missing	727 (96.2%)	13 (92.9%)	29 (96.7%)	62 (100%)

	France All patients (N=1,384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
Clinical laboratory tests: ALT (Female) (IU/L)*				
N	37 (5.9%)	none	PPD	PPD
< 2*ULNR	PPD	none	PPD	PPD
≥2*ULNR	PPD	none	none	none
Mean (SD)	36.5 (29.1)	-	37 (22.6)	23 (11.1)
Min-Max	9 - 136	-	16 - 72	13 - 35
Median [Q1-Q3]	28 [21 - 40]	-	28 [20 - 58]	21 [13 - 35]
Missing	591 (94.1%)	7 (100%)	32 (84.2%)	68 (95.8%)
Clinical laboratory tests: ALT (Male) (IU/L)*				
N	33 (4.4%)	PPD	PPD	PPD
< 2*ULNR	PPD	PPD	PPD	PPD
≥2*ULNR	PPD	none	none	none
Mean (SD)	39.6 (22.7)	23.5 (7.8)	68 (n/a)	16.5 (2.1)
Min-Max	15 - 103	18 - 29	68 - 68	15 - 18
Median [Q1-Q3]	29 [21 - 54]	23.5 [18 - 29]	68 [68 - 68]	16.5 [15 - 18]
Missing	723 (95.6%)	12 (85.7%)	29 (96.7%)	60 (96.8%)

* Derived variable
AST: aspartate amino transferase; ALT: alanine amino transferase; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HDL: high density lipoprotein; LDL: low density lipoprotein; SD: standard deviation
Subgroup of patients with hepatic disease has not been presented due to privacy morns (i.e. N<10)
For computation of Missing patients, n/N=number of missing patients/total population, n/a=not applicable to report SD as N=1
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset France, Table T_06

10.2.3.2.2. Germany

Details of the overall population in Germany are presented in Table 10.2.3-3. Across the study groups, at least 85% of dulaglutide initiators reported HbA1c >7.5% with a mean value ranging between 9.4% to 10.1%. Patients with a history of hepatic disease had the highest mean HbA1c (10.1%). More than 97% of patients with histories of heart failure, hepatic disease, severe GI disease, and patients aged ≥75 years had eGFR values that were ≥30 mL/min/1.73 m^2. The mean value ranged between 55.9 and 131.6 mL/min/1.73 m^2 with the highest reported in patients with pre-existing hepatic disease, while patients with severe renal failure were reported to have the lowest mean value.

Serum creatinine values of <100 µmol/L were reported highest among female dulaglutide initiators with a history of severe GI disease, whereas most of the male patients with a history of hepatic disease had serum creatinine values of <120 µmol/L. Patients aged ≥75 years had mean serum creatinine values of 101.1 µmol/L in females and 109.3 µmol/L in males.

A majority of dulaglutide initiators had LDL cholesterol <1.6 g/L (ranging from 50% to 64%) with comparable mean values across all subgroups (1.4-1.6 g/L). With the exception of patients with pre-existing severe renal failure, a higher proportion of patients had HDL cholesterol ≥0.35 g/L (ranging from 53% to 64%; 45% in patients with severe renal failure) with similar mean values across all subgroups (0.4 g/L).

AST values of <2*ULNR were reported highest among 92% of women with a history of severe GI disease and all men with a history of severe renal failure. However, patients with a history of hepatic disease had a higher mean AST value (61.2 IU/L in females and 60.3 IU/L in males). ALT values of <2*ULNR were reported highest in women dulaglutide initiators aged ≥75 years (89.9%) and all men initiators with a history of severe renal failure. Patients with pre-existing hepatic disease had a higher mean ALT value (71.6 IU/L in females and 72.5 IU/L in males).

Table 10.2.3-3 Description of the clinical laboratory tests reported per subgroup in Germany

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Clinical laboratory tests: HbA1c (%) *						
N	2,989 (62.8%)	20 (76.9%)	346 (68.8%)	100 (66.2%)	290 (75.1%)	301 (62.2%)
≤ 6.5%	162 (5.4%)	PPD			15 (5.2%)	PPD
6.6% - 7.5%	266 (8.9%)	PPD	PPD	PPD	21 (7.2%)	PPD
>7.5%	2,561 (85.7%)	17 (85%)	313 (90.5%)	92 (92%)	254 (87.6%)	272 (90.4%)
Mean (SD)	9.5 (1.9)	9.8 (1.7)	9.6 (1.9)	10.1 (2)	9.4 (1.8)	9.5 (1.7)
Min-Max	5 - 17.7	6.2 - 12.4	5.6 - 16.7	6 - 14.8	5.6 - 15.1	5.9 - 15.4
Median [Q1-Q3]	9.3 [8.2 - 10.7]	9.8 [8.8 - 11.3]	9.5 [8.3 - 10.7]	9.9 [8.7 - 11.6]	9.3 [8.2 - 10.5]	9.2 [8.3 - 10.4]
Missing	1,770 (37.2%)	6 (23.1%)	157 (31.2%)	51 (33.8%)	96 (24.9%)	183 (37.8%)
Clinical laboratory tests: eGFR (mL/min/1.73 m^2*)						
N	1,127 (23.7%)	10 (38.5%)	134 (26.6%)	38 (25.2%)	101 (26.2%)	91 (18.8%)
< 30 mL/min/1.73 m^2	PPD			none	none	PPD
≥30 mL/min/1.73 m^2	PPD	PPD	PPD	38 (100%)	101 (100%)	PPD
Mean (SD)	131.4 (54.7)	55.9 (33.8)	111.9 (47.2)	131.6 (47.6)	116.5 (45.5)	67.2 (19.1)
Min-Max	12.8 - 431	12.8 - 128.2	26.5 - 276	41.8 - 223.4	48.5 - 245.4	26.5 - 110.2
Median [Q1-Q3]	123.7 [91.8 - 160.8]	42.2 [39.9 - 78.2]	106.4 [78.3 - 133.8]	132.8 [95.6 - 162.1]	110.4 [82.2 - 134.5]	66.4 [52.9 - 81.4]

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Missing	36,32 (76.3%)	16 (61.5%)	369 (73.4%)	113 (74.8%)	285 (73.8%)	393 (81.2%)
Clinical laboratory tests: Serum creatinine (female)(µmol/L)*						
N	487 (22.9%)	PPD	50 (25.9%)	18 (31.6%)	45 (24.7%)	47 (18.7%)
< 100 µmol/L	432 (88.7%)	none	PPD	PPD	PPD	24 (51.1%)
≥100 µmol/L	55 (11.3%)	PPD	PPD	PPD	PPD	23 (48.9%)
Mean (SD)	74.2 (23.9)	150.8 (23)	87.3 (31.3)	79.9 (34.3)	72.7 (21.9)	101.1 (28)
Min-Max	33.6 - 185.9	129.2 - 185.9	52.2 - 166.4	50.4 - 159.3	44.3 - 150.5	52.2 - 163.7
Median [Q1-Q3]	69.9 [58.4 - 83.2]	146.9 [132.8 - 159.3]	80.1 [62 - 97.4]	64.6 [57.5 - 91.2]	69 [57.5 - 79.7]	94.7 [79.7 - 123]
Missing	1,642 (77.1%)	7 (58.3%)	143 (74.1%)	39 (68.4%)	137 (75.3%)	204 (81.3%)
Clinical laboratory tests: Serum creatinine (male)(µmol/L)*						
N	640 (24.3%)	PPD	84 (27.1%)	20 (21.3%)	56 (27.5%)	44 (18.9%)
< 120 µmol/L	555 (86.7%)	PPD	60 (71.4%)	PPD	PPD	32 (72.7%)
≥120 µmol/L	85 (13.3%)	PPD	24 (28.6%)	PPD	PPD	12 (27.3%)
Mean (SD)	93.7 (32.1)	220.7 (183.6)	105 (29.8)	89.5 (41.5)	96 (21.4)	109.3 (26.6)
Min-Max	42.5 - 539.9	74.3 - 539.9	48.7 - 185.9	56.6 - 251.3	59.3 - 145.1	67.3 - 185.9
Median [Q1-Q3]	88.5 [75.2 - 103.5]	154 [140.7 - 194.7]	97.4 [82.7 - 123]	82.3 [66.4 - 93.4]	91.6 [79.7 - 109.7]	107.1 [87.6 - 125.2]
Missing	1,990 (75.7%)	9 (64.3%)	226 (72.9%)	74 (78.7%)	148 (72.5%)	189 (81.1%)
Urine albumin positive*	-	-	-	-	-	-
Clinical laboratory tests: LDL cholesterol (g/L)*						
N	3,007 (63.2%)	20 (76.9%)	329 (65.4%)	94 (62.3%)	291 (75.4%)	301 (62.2%)
< 1.6 g/L	1,938 (64.4%)	PPD	212 (64.4%)	47 (50%)	178 (61.2%)	193 (64.1%)
≥1.6 g/L	1,069 (35.6%)	PPD	117 (35.6%)	47 (50%)	113 (38.8%)	108 (35.9%)
Mean (SD)	1.5 (1.5)	1.5 (0.6)	1.4 (0.5)	1.5 (0.5)	1.5 (0.4)	1.6 (2.6)
Min-Max	0 - 65.3	0.7 - 3.4	0 - 3	0.5 - 2.8	0 - 2.9	0 - 45.2
Median [Q1-Q3]	1.4 [1.2 - 1.7]	1.4 [1 - 1.9]	1.4 [1.1 - 1.7]	1.6 [1.3 - 1.8]	1.5 [1.2 - 1.7]	1.4 [1.1 - 1.8]

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Missing	1,752 (36.8%)	6 (23.1%)	174 (34.6%)	57 (37.7%)	95 (24.6%)	183 (37.8%)
Clinical laboratory tests: HDL cholesterol (g/L)*						
N	3,102 (65.2%)	20 (76.9%)	344 (68.4%)	99 (65.6%)	296 (76.7%)	301 (62.2%)
< 0.35 g/L	1,160 (37.4%)	PPD	161 (46.8%)	44 (44.4%)	120 (40.5%)	108 (35.9%)
≥ 0.35 g/L	1,942 (62.6%)	PPD	183 (53.2%)	55 (55.6%)	176 (59.5%)	193 (64.1%)
Mean (SD)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)
Min-Max	0 - 1	0.2 - 0.5	0 - 1	0 - 0.8	0 - 1	0 - 1
Median [Q1-Q3]	0.4 [0.3 - 0.4]	0.3 [0.3 - 0.4]	0.4 [0.3 - 0.4]	0.4 [0.3 - 0.4]	0.4 [0.3 - 0.4]	0.4 [0.3 - 0.5]
Missing	1,657 (34.8%)	6 (23.1%)	159 (31.6%)	52 (34.4%)	90 (23.3%)	183 (37.8%)
Clinical laboratory tests: AST (Female) (IU/L)*						
N	972 (45.7%)	PPD	88 (45.6%)	31 (54.4%)	112 (61.5%)	114 (45.4%)
< 2*ULNR	890 (91.6%)	PPD	76 (86.4%)	PPD	PPD	PPD
≥2*ULNR	82 (8.4%)	PPD	12 (13.6%)	PPD	PPD	PPD
Mean (SD)	37.4 (31.4)	46.3 (32.8)	44.1 (46.5)	61.2 (70.8)	38 (23)	36.9 (27.9)
Min-Max	0.2 – 392	19 – 104	0.5 – 392	0.4 – 392	0.6 – 163	0.3 – 210
Median [Q1-Q3]	29 [22 – 43.1]	36 [20 – 63.0]	30.5 [23 – 52]	44 [25 – 63]	30 [24 – 43]	29 [22.9 – 43]
Missing	1,157 (54.3%)	6 (50%)	105 (54.4%)	26 (45.6%)	70 (38.5%)	137 (54.6%)
Clinical laboratory tests: AST (Male) (IU/L)*						
N	1,188 (45.2%)	PPD	152 (49%)	47 (50%)	113 (55.4%)	112 (48.1%)
< 2*ULNR	1,122 (94.4%)	PPD	144 (94.7%)	39 (83%)	103 (91.2%)	109 (97.3%)
≥2*ULNR	66 (5.6%)	none	8 (5.3%)	8 (17%)	10 (8.8%)	3 (2.7%)
Mean (SD)	41.3 (44)	31.4 (17.3)	40.2 (27.4)	60.3 (37.1)	44.8 (27.3)	35.3 (23.6)
Min-Max	0.2 – 1,065	15 - 69	0.4 - 197	1.2 - 197	0.3 - 145	0.3 - 155
Median [Q1-Q3]	32.2 [24 - 48]	30 [20 - 32]	32 [25 - 48]	56 [30.6 - 80]	36 [28 - 55]	31 [23.5 - 41]
Missing	1,442 (54.8%)	5 (35.7%)	158 (51%)	47 (50%)	91 (44.6%)	121 (51.9%)

	Germany All patients (N=4,759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
Clinical laboratory tests: ALT (Female) (IU/L)*						
N	1,042 (48.9%)	PPD	98 (50.8%)	33 (57.9%)	117 (64.3%)	119 (47.4%)
< 2*ULNR	884 (84.8%)	PPD	78 (79.6%)	PPD	93 (79.5%)	107 (89.9%)
≥2*ULNR	158 (15.2%)	PPD	20 (20.4%)	PPD)	24 (20.5%)	12 (10.1%)
Mean (SD)	47.4 (39.4)	49.8 (35.6)	50.3 (34.1)	71.6 (63.3)	54.7 (45.3)	41.2 (35.1)
Min-Max	0.2 - 346	18 - 107	0.5 - 186	0.4 - 346	1 - 300	0.2 - 206
Median [Q1-Q3]	38 [24 - 57]	41.5 [21 - 70]	40.5 [28 - 64]	60 [31 - 82]	43 [28.8 - 66]	35 [21 - 49]
Missing	1,087 (51.1%)	6 (50%)	95 (49.2%)	24 (42.1%)	65 (35.7%)	132 (52.6%)
Clinical laboratory tests: ALT (Male) (IU/L)*						
N	1,298 (49.4%)	PPD	164 (52.9%)	48 (51.1%)	116 (56.9%)	116 (49.8%)
< 2*ULNR	1,145 (88.2%)	PPD	151 (92.1%)	PPD	103 (88.8%)	PPD
≥2*ULNR	153 (11.8%)	none	13 (7.9%)	PPD	13 (11.2%)	PPD
Mean (SD)	56.9 (51.9)	37.7 (16.3)	53.7 (46)	72.5 (49.9)	62.7 (42.5)	43 (28.4)
Min-Max	0.2 - 728	18 - 73	0.6 - 351	0.6 - 326	0.4 - 351	0.4 - 163
Median [Q1-Q3]	45 [31 - 69]	32 [30 - 43.5]	42 [31 - 61.5]	62.5 [44 - 91]	54 [39 - 74]	37 [25.4 - 56]
Missing	1,332 (50.6%)	5 (35.7%)	146 (47.1%)	46 (48.9%)	88 (43.1%)	117 (50.2%)

* Derived variable
AST: aspartate amino transferase; ALT: alanine amino transferase; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HDL: high density lipoprotein; LDL: low density lipoprotein; SD: standard deviation
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Germany, Table T_06

10.2.3.2.3. Spain

Details of the overall population in Spain are presented in Table 10.2.3-4. More than 84% of dulaglutide initiators in Spain were reported as having HbA1c >7.5% with similar mean values across the study groups (9.2% to 9.6%). More than 93% of patients with histories of heart failure, hepatic disease, severe GI disease, and patients aged ≥75 years had eGFR values ≥30 mL/min/1.73 m^2. All dulaglutide initiators with pre-existing severe renal failure had eGFR < 30 mL/min/1.73 m^2. The mean value ranged between 23.4 and 74 mL/min/1.73 m^2 with the highest reported in patients with a history of hepatic disease.

More than half of women dulaglutide initiators with histories of heart failure, hepatic disease and severe GI disease had serum creatinine values of <100 µmol/L; whereas women with pre-

existing severe renal failure and women aged ≥75 years had serum creatinine values of ≥100 µmol/L. A similar trend was observed among men dulaglutide initiators where the proportion of serum creatinine values <100 µmol/L were equal to or higher across the same subgroups. Mean serum creatinine values for patients with pre-existing severe renal failure were166.5 µmol/L in females and 249.0 µmol/L in males.

Across all study subgroups, more than 50% of patients had UACR <30 mg/g except for those with a history of severe renal failure, in which 77.8% of patients had UACR ≥30 mg/g. Patients with severe renal failure had the highest mean UACR (602.7 mg/g) whereas patients with hepatic disease had the lowest mean UACR (116.1 mg/g).

More than 86% of patients had LDL cholesterol <1.6 g/L across all the study groups, of which, patients with heart failure had the highest proportion (93.5%). Dulaglutide initiators aged ≥75 years had the highest mean LDL cholesterol (3.5 g/L). A majority of patients across all study subgroups had HDL cholesterol ≥0.35 g/L (ranging from 65% to 79%) in which patients aged ≥75 years had the highest proportion. Patients with a history of heart failure had the highest mean HDL cholesterol (1.25 g/L).

AST values of <2*ULNR were reported in more than 88% of women and 89% of men across the subgroups. Dulaglutide initiators with pre-existing hepatic disease had the highest mean AST value (42.4 IU/L in females and 46.8 IU/L in males). Similarly, ALT values of <2*ULNR were reported in more than 88% of women and 86% of men across the subgroups. Female patients with pre-existing heart failure and male patients with pre-existing severe GI disease had the highest proportion (98.4% and 96.9%, respectively). The mean ALT values among women and men were 45.1 IU/L and 57.9 IU/L, respectively.

Table 10.2.3-4 Description of the clinical laboratory tests reported per subgroup in Spain

	Spain All patients (N=2,716)	**Severe renal failure (N=36)**	**Heart failure (N=178)**	**Hepatic disease (N=451)**	**Severe GI disease (N=287)**	**Aged ≥75 (N=213)**
Clinical laboratory tests: HbA1c (%)*						
N	2,370 (87.3%)	34 (94.4%)	154 (86.5%)	408 (90.5%)	250 (87.1%)	189 (88.7%)
≤ 6.5%	99 (4.2%)	none	PPD	17 (4.2%)	PPD	PPD
6.6% - 7.5%	207 (8.7%)	PPD	PPD	46 (11.3%)	PPD	PPD
>7.5%	2,064 (87.1%)	PPD	129 (83.8%)	345 (84.6%)	212 (84.8%)	173 (91.5%)
Mean (SD)	9.4 (1.8)	9.4 (1.7)	9.4 (1.9)	9.3 (1.8)	9.2 (1.7)	9.6 (1.5)
Min-Max	4.8 - 17.1	6.7 - 14.2	5.8 - 17.1	5.6 - 15.5	4.8 - 14	5.8 - 13.7
Median [Q1-Q3]	9.3 [8.2 - 10.5]	9.5 [8 - 10.3]	9.2 [8.1 - 10.6]	9.2 [8.1 - 10.6]	9 [8.1 - 10.2]	9.6 [8.5 - 10.6]
Missing	346 (12.7%)	2 (5.6%)	24 (13.5%)	43 (9.5%)	37 (12.9%)	24 (11.3%)
Clinical laboratory tests: eGFR (mL/min/1.73 m^2*)						
N	1,752 (64.5%)	27 (75%)	113 (63.5%)	294 (65.2%)	190 (66.2%)	143 (67.1%)

	Spain All patients (N=2,716)	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
< 30 mL/min/1.73 m^2	29 (1.7%)	27 (100%)	PPD	PPD	PPD	PPD
≥ 30 mL/min/1.73 m^2	1,723 (98.3%)	none	PPD	PPD	PPD	PPD
Mean (SD)	71.2 (19.5)	23.4 (5.9)	59.9 (21)	74 (18.4)	67.6 (20.4)	55.3 (17.7)
Min-Max	4.4 - 132.5	4.4 - 29.7	4.4 - 105	20.1 - 119.6	4.4 - 116	9.5 - 93
Median [Q1-Q3]	66 [60 - 90]	25.2 [21.1 - 26.9]	60 [45.5 - 74.6]	75 [60 - 90]	60 [57.3 - 88.1]	55.7 [42 - 61]
Missing	964 (35.5%)	9 (25%)	65 (36.5%)	157 (34.8%)	97 (33.8%)	70 (32.9%)
Clinical laboratory tests: Serum creatinine (female) (µmol/L)*						
N	1,224 (89.9%)	PPD	68 (89.5%)	226 (91.1%)	124 (91.9%)	123 (91.1%)
< 100 µmol/L	898 (73.4%)	PPD	36 (52.9%)	170 (75.2%)	71 (57.3%)	51 (41.5%)
≥100 µmol/L	326 (26.6%)	PPD	32 (47.1%)	56 (24.8%)	53 (42.7%)	72 (58.5%)
Mean (SD)	73.9 (24.8)	166.5 (53.7)	88.7 (39.2)	71.9 (20.2)	82.6 (30.6)	87.9 (28.3)
Min-Max	0.6 - 212.2	2 - 212.2	1.1 - 212.2	0.7 - 185.7	0.6 - 194.5	1.5 - 209.6
Median [Q1-Q3]	70.7 [61 - 83.1]	176.8 [162.7 - 194.5]	79.6 [70.7 - 106.1]	70.7 [61.9 - 79.6]	73.8 [61.9 - 97.3]	88.4 [70.7 - 103.5]
Missing	137 (10.1%)	1 (7.1%)	8 (10.5%)	22 (8.9%)	11 (8.1%)	12 (8.9%)
Clinical laboratory tests: Serum creatinine (male) (µmol/L)* ¶						
N	1175 (86.7%)	22 (100%)	88 (86.3%)	184 (90.6%)	134 (88.2%)	70 (89.7%)
< 120 µmol/L	832 (70.8%)	none	44 (50%)	137 (74.5%)	81 (60.4%)	28 (40%)
≥120 µmol/L	343 (29.2%)	22 (100%)	44 (50%)	47 (25.5%)	53 (39.6%)	42 (60%)
Mean (SD)	96.4 (39.5)	249 (108.4)	115 (67.7)	93.8 (34.8)	102.9 (33.3)	130.9 (67)
Min-Max	0.7 - 618.1	106.1 - 618.1	1 - 618.1	0.7 - 265.3	61.9 - 265.3	1 - 482.8
Median [Q1-Q3]	88.4 [76.9 - 106.1]	229.5 [203.4 - 245.8]	101.7 [87.5 - 131.3]	88.4 [76.9 - 106.1]	97.3 [79.6 - 119.4]	116.3 [89.3 - 165.3]
Missing	180 (13.3%)	none	14 (13.7%)	19 (9.4%)	18 (11.8%)	8 (10.3%)
Urine albumin positive*	380 (35.8%)	12 (70.6%)	35 (49.3%)	62 (30.2%)	47 (37%)	30 (46.2%)
Clinical laboratory tests: UACR (mg/g)*						
N	1,907 (70.2%)	27 (75%)	122 (68.5%)	319 (70.7%)	204 (71.1%)	149 (70%)
< 30 mg/g	1,190 (62.4%)	PPD	62 (50.8%)	203 (63.6%)	126 (61.8%)	79 (53%)
≥30 mg/g	717 (37.6%)	PPD	60 (49.2%)	116 (36.4%)	78 (38.2%)	70 (47%)
Mean (SD)	130.1 (350.1)	602.7 (747.7)	229.3 (517.1)	116.1 (336.8)	148.5 (369.9)	173.9 (391)
Min-Max	0 – 2,999.2	5 – 2,410.5	0.8 – 2,453.8	1.1 – 2,999.2	0.8 – 2,863	1.2 – 2,453.8

	Spain All patients (N=2,716)	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
Median [Q1-Q3]	16.8 [6.1 - 69.5]	255.8 [30.5 - 1048]	29.7 [6.7 - 141.4]	14.1 [5.9 - 56.3]	17 [6.2 - 88.5]	24.9 [7.3 - 122]
Missing	809 (29.8%)	9 (25%)	56 (31.5%)	132 (29.3%)	83 (28.9%)	64 (30%)
Clinical laboratory tests: LDL cholesterol (g/L)* ¶						
N	2,239 (82.4%)	31 (86.1%)	139 (78.1%)	376 (83.4%)	235 (81.9%)	182 (85.4%)
< 1.6 g/L	1,995 (89.1%)	PPD	PPD	326 (86.7%)	211 (89.8%)	169 (92.9%)
≥1.6 g/L	244 (10.9%)	PPD	PPD	50 (13.3%)	24 (10.2%)	13 (7.1%)
Mean (SD)	2.6 (13.5)	0.9 (0.4)	3.3 (16.4)	2.1 (9.2)	1.7 (8.8)	3.5 (17.3)
Min-Max	0.2 - 185	0.3 - 2	0.3 - 155	0.3 - 120	0.3 - 136	0.2 - 155
Median [Q1-Q3]	1.1 [0.9 - 1.4]	0.9 [0.7 - 1.1]	1 [0.8 - 1.3]	1.1 [0.9 - 1.4]	1.1 [0.8 - 1.3]	1 [0.8 - 1.2]
Missing	477 (17.6%)	5 (13.9%)	39 (21.9%)	75 (16.6%)	52 (18.1%)	31 (14.6%)
Clinical laboratory tests: HDL cholesterol (g/L)* ¶						
N	2,369 (87.2%)	34 (94.4%)	154 (86.5%)	404 (89.6%)	250 (87.1%)	187 (87.8%)
< 0.35 g/L	717 (30.3%)	PPD	52 (33.8%)	129 (31.9%)	81 (32.4%)	39 (20.9%)
≥ 0.35 g/L	1,652 (69.7%)	PPD	102 (66.2%)	275 (68.1%)	169 (67.6%)	148 (79.1%)
Mean (SD)	0.9 (4.6)	0.36 (0.09)	1.25 (5.35)	0.74 (3.53)	0.55 (2.38)	1.12 (4.77)
Min-Max	0.1 - 64	0.2 - 0.6	0.1 - 41	0.2 - 53	0.2 - 38	0.2 - 41
Median [Q1-Q3]	0.4 [0.3 - 0.5]	0.4 [0.3 - 0.4]	0.4 [0.3 - 0.5]	0.4 [0.3 - 0.5]	0.4 [0.3 - 0.5]	0.4 [0.4 - 0.5]
Missing	347 (12.8%)	2 (5.6%)	24 (13.5%)	47 (10.4%)	37 (12.9%)	26 (12.2%)
Clinical laboratory tests: AST (Female) (IU/L)*						
N	701 (51.5%)	PPD	38 (50%)	170 (68.5%)	76 (56.3%)	58 (43%)
< 2*ULNR	646 (92.2%)	PPD	PPD	150 (88.2%)	PPD	PPD
≥2*ULNR	55 (7.8%)	none	PPD	20 (11.8%)	PPD	PPD
Mean (SD)	33.8 (25.8)	32.2 (14.4)	27.2 (13.1)	42.4 (36.6)	34.3 (33.1)	29.6 (19.7)
Min-Max	8 - 287	13 - 59	8 - 81	8 - 287	13 - 287	8 - 112
Median [Q1-Q3]	25 [19 - 39]	31 [20 - 41]	23.5 [21 - 34]	31 [22 - 49]	27.5 [20 - 37.5]	22 [18 - 36]
Missing	660 (48.5%)	4 (28.6%)	38 (50%)	78 (31.5%)	59 (43.7%)	77 (57%)
Clinical laboratory tests: AST (Male) (IU/L)*						
N	697 (51.4%)	15 (68.2%)	52 (51%)	140 (69%)	74 (48.7%)	35 (44.9%)
< 2*ULNR	669 (96%)	PPD	PPD	125 (89.3%)	74 (100%)	PPD
≥2*ULNR	28 (4%)	PPD	PPD	15 (10.7%)	none	PPD
Mean (SD)	35.2 (21.9)	37.8 (27.1)	31.6 (17.8)	46.8 (26.4)	31.8 (17)	33.4 (20.5)
Min-Max	7 - 162	16 - 110	8 - 91	11 - 130	13 - 89	13 - 92
Median [Q1-Q3]	28 [21 - 43]	28 [20 - 49]	25.5 [19.5 - 39.5]	39 [26.5 - 61.5]	26 [20 - 40]	24 [20 - 44]
Missing	658 (48.6%)	7 (31.8%)	50 (49%)	63 (31%)	78 (51.3%)	43 (55.1%)

	Spain All patients (N=2,716)	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
Clinical laboratory tests: ALT (Female) (IU/L)*						
N	1,175 (86.3%)	12 (85.7%)	63 (82.9%)	225 (90.7%)	120 (88.9%)	119 (88.1%)
< 2*ULNR	1,101 (93.7%)	PPD	PPD	198 (88%)	PPD	PPD
≥2*ULNR	74 (6.3%)	PPD	PPD	27 (12%)	PPD	PPD
Mean (SD)	35 (27.1)	35.3 (21.6)	28.4 (17.4)	45.1 (37.8)	33.2 (24.4)	26.6 (18.7)
Min-Max	8 - 306	10 - 74	10 - 118	10 - 306	8 - 207	10 - 163
Median [Q1-Q3]	27 [19 - 40]	26.5 [18.5 - 51.5]	25 [17 - 34]	34 [23 - 52]	26.5 [19.5 - 37]	20 [16 - 32]
Missing	186 (13.7%)	2 (14.3%)	13 (17.1%)	23 (9.3%)	15 (11.1%)	16 (11.9%)
Clinical laboratory tests: ALT (Male) (IU/L)*						
N	1,129 (83.3%)	21 (95.5%)	84 (82.4%)	180 (88.7%)	129 (84.9%)	65 (83.3%)
< 2*ULNR	1,063 (94.2%)	PPD	PPD	154 (85.6%)	PPD	PPD
≥2*ULNR	66 (5.8%)	PPD	PPD	26 (14.4%)	PPD	PPD
Mean (SD)	41.9 (28.3)	34.5 (22.3)	34.7 (26.5)	57.9 (35.5)	36 (22.5)	34.3 (30)
Min-Max	8 - 286	12 - 102	8 - 180	13 - 212	8 - 150	9 - 180
Median [Q1-Q3]	34 [24 - 51]	31 [18 - 44]	27 [19 - 42.5]	49 [32.5 - 73.5]	31 [22 - 44]	24 [18 - 36]
Missing	226 (16.7%)	1 (4.5%)	18 (17.6%)	23 (11.3%)	23 (15.1%)	13 (16.7%)

* Derived variable
AST: aspartate amino transferase; ALT: alanine amino transferase; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HDL: high density lipoprotein; LDL: low density lipoprotein; SD: standard deviation; UACR: urine albumin/creatinine ratio
For computation of Missing patients, n/N=number of missing patients/total population
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset Spain, Table T_06

10.2.3.2.4. UK

Details of the overall population in the UK are presented in Table 10.2.3-5. More than 87% of dulaglutide initiators reported HbA1c >7.5% with similar mean values (9.3% to 9.8%) across the study groups among which patients with pre-existing heart failure had the highest proportion (94.1%). More than 92% of patients had eGFR values ≥30 mL/min/1.73 m^2 across the study groups among which patients with a history of hepatic disease had the highest proportion (98.9%). The mean eGFR value ranged between 56 and 68 mL/min/1.73 m^2 with the highest reported in patients with a history of hepatic disease.

Approximately 91% of women with pre-existing hepatic disease, 89% of women with a history of severe GI disease, and 65% of women aged ≥75 years had serum creatinine values of <100 µmol/L with corresponding mean values of 67.6, 72.7, and 92.8 µmol/L, respectively. Among men dulaglutide initiators, a majority of the patients with severe GI disease (87.9%), hepatic disease (86.7%), heart failure (52.0%), and men aged ≥75 years (60.7%) had serum creatinine

value of <120 µmol/L. Patients with pre-existing heart failure had the highest mean serum creatinine values (114.7 µmol/L).

Across all study groups, more than 55% of patients had UACR <30 mg/g except for those patients aged ≥75 years, among which 57.1% of patients had UACR ≥30 mg/g. Elderly patients had the highest mean UACR (180.7 mg/g), whereas patients with a history of heart failure had the lowest mean UACR (27.8 mg/g).

More than 81% of patients had LDL cholesterol <1.6 g/L across all the study groups in which elderly patients aged ≥75 years had the highest proportion (91.9%). Mean LDL cholesterol was comparable across all subgroups (1.0-1.2 g/L). A majority of patients across all study groups had HDL cholesterol ≥0.35 g/L (ranging from 56% to 74%) in which patients aged ≥75 years had the highest proportion. Mean HDL cholesterol was similar across all subgroups of dulaglutide initiators (0.4 g/L).

Among women who started treatment with dulaglutide, all aged ≥75 years, and the vast majority of those with histories of severe GI disease (96.1%), hepatic disease (85.3%), and heart failure (83.3%) had ALT values of <2*ULNR with corresponding ALT mean values of 18.7, 29.9, 33.9, and 24 IU/L, respectively. A similar majority among men initiators of dulaglutide was observed to have ALT values <2*ULNR among all men ≥75 years old, all patients with heart failure, about 99% of those with severe GI disease, and 98% of those with hepatic disease. The corresponding ALT mean values were 25.1, 30.5, 33.1, and 39.8 IU/L, respectively.

Table 10.2.3-5 Description of the clinical laboratory tests reported per subgroup in the UK

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
Clinical laboratory tests: HbA1c (%)*					
N	1,193 (91.5%)	34 (81%)	92 (92%)	216 (92.3%)	55 (90.2%)
≤ 6.5%	31 (2.6%)	PPD	PPD	PPD	PPD
6.6% - 7.5%	98 (8.2%)	PPD	PPD	PPD	PPD
>7.5%	1,064 (89.2%)	PPD	82 (89.1%)	193 (89.4%)	PPD
Mean (SD)	9.4 (1.7)	9.8 (1.6)	9.3 (1.4)	9.3 (1.6)	9.4 (1.7)
Min-Max	2.6 - 17.3	6.2 - 13	5.5 - 12.1	5.9 - 17.3	6.1 - 17.3
Median [Q1-Q3]	9.3 [8.3 - 10.5]	9.65 [8.4 - 11]	9.4 [8.4 - 10.3]	9.1 [8.4 - 10.3]	9 [8.4 - 10.2]
Missing	111 (8.5%)	8 (19%)	8 (8%)	18 (7.7%)	6 (9.8%)
Clinical laboratory tests: eGFR (mL/min/1.73 m2*)					
N	1,087 (83.4%)	35 (83.3%)	87 (87%)	199 (85%)	54 (88.5%)
< 30 mL/min/1.73 m^2	58 (5.3%)	PPD	PPD	PPD	PPD
≥ 30 mL/min/1.73 m^2	1,029 (94.7%)	PPD	PPD	PPD	PPD
Mean (SD)	69.2 (22.2)	56 (17.4)	68 (16.9)	66.3 (21.9)	56.4 (19.4)

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
Min-Max	0.7 - 115	22 - 90	1 - 101	0.8 - 112	0.8 - 90
Median [Q1-Q3]	72 [60 - 90]	57 [41 - 63]	60 [60 - 88]	63 [60 - 8]	59.5 [43 - 72]
Missing	217 (16.6%)	7 (16.7%)	13 (13.0%)	35 (15.0%)	7 (11.5%)
Clinical laboratory tests: Serum creatinine (female) (µmol/L)*					
N	510 (83.2%)	12 (75%)	42 (85.7%)	102 (89.5%)	26 (89.7%)
< 100 µmol/L	467 (91.6%)	PPD	PPD	PPD	PPD
≥100 µmol/L	43 (8.4%)	PPD	PPD	PPD	PPD
Mean (SD)	71.1 (19.1)	99.8 (37.3)	67.6 (18.0)	72.7 (20.7)	92.8 (33)
Min-Max	33 - 187	61 - 187	39 - 110	40 - 165	53 - 187
Median [Q1-Q3]	67 [59 - 79]	93 [70 - 120.5]	64 [57 - 71]	66.5 [60 - 82]	89 [69 - 111]
Missing	103 (16.8%)	4 (25%)	7 (14.3%)	12 (10.5%)	3 (10.3%)
Clinical laboratory tests: Serum creatinine (male) (µmol/L)*					
N	584 (84.5%)	25 (96.2%)	45 (88.2%)	99 (82.5%)	28 (87.5%)
< 120 µmol/L	522 (89.4%)	13 (52%)	PPD	87 (87.9%)	PPD
≥120 µmol/L	62 (10.6%)	12 (48%)	PPD	12 (12.1%)	PPD
Mean (SD)	88.9 (24.3)	114.7 (36.7)	87.4 (21.5)	90.5 (23.7)	111 (37.4)
Min-Max	38 - 229	54 - 193	52 - 138	38 - 160	59 - 221
Median [Q1-Q3]	84 [72.5 - 99]	116 [83 - 142]	8 [74 - 96]	89 [74 - 104]	99 [83.5 - 130]
Missing	107 (15.5%)	1 (3.8%)	6 (11.8%)	21 (17.5%)	4 (12.5%)
Urine albumin positive*	11 (26.8%)	1 (33.3%)	1 (33.3%)	2 (28.6%)	none
Clinical laboratory tests: UACR (mg/g)*					
N	471 (36.1%)	15 (35.7%)	43 (43.0%)	88 (37.6%)	21 (34.4%)
< 30 mg/g	304 (64.5%)	PPD	24 (55.8%)	52 (59.1%)	PPD
≥30 mg/g	167 (35.5%)	PPD	19 (44.2%)	36 (40.9%)	PPD
Mean (SD)	107.1 (499.7)	27.8 (44.2)	119.1 (342.1)	159.2 (608.2)	180.7 (450.7)
Min-Max	0 – 7,823.4	3.5 - 179.7	0 – 2,125.8	0 – 5,247.2	0 – 2,044.4
Median [Q1-Q3]	18.6 [8.9 - 45.1]	16.8 [6.2 - 23]	22.1 [9.7 - 51.2]	22.1 [11.1 - 59.3]	39.8 [17.7 - 76.1]
Missing	833 (63.9%)	27 (64.3%)	57 (57%)	146 (62.4%)	40 (65.6%)
Clinical laboratory tests: LDL cholesterol (g/L)*¶					
N	784 (60.1%)	22 (52.4%)	58 (58%)	132 (56.4%)	37 (60.7%)
< 1.6 g/L	658 (83.9%)	PPD	PPD	112 (84.8%)	PPD
≥1.6 g/L	126 (16.1%)	PPD	PPD	20 (15.2%)	PPD
Mean (SD)	1.2 (0.5)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1 (0.4)

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
Min-Max	0.2 - 5.4	0.7 - 2.1	0.4 - 2.9	0.3 - 2.7	0.3 - 2
Median [Q1-Q3]	1.1 [0.9 - 1.4]	1 [0.9 - 1.5]	1.1 [0.9 - 1.4]	14 [0.9 - 1.3]	1 [0.8 - 1.2]
Missing	520 (39.9%)	20 (47.6%)	42 (42%)	102 (43.6%)	24 (39.3%)
Clinical laboratory tests: HDL cholesterol (g/L)*¶					
N	892 (68.4%)	25 (59.5%)	66 (66%)	154 (65.8%)	43 (70.5%)
< 0.35 g/L	259 (29%)	PPD	23 (34.8%)	48 (31.2%)	PPD
≥ 0.35 g/L	633 (71%)	PPD	43 (65.2%)	106 (68.8%)	PPD
Mean (SD)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)
Min-Max	0.2 - 1.5	0.3 - 0.5	0.2 - 0.8	0.2 - 0.8	0.2 - 0.6
Median [Q1-Q3]	0.4 [0.3 - 0.5]	0.4 [0.3 - 0.4]	0.4 [0.3 - 0.5]	0.4 [0.3 - 0.5]	0.4 [0.3 - 0.5]
Missing	412 (31.6%)	17 (40.5%)	34 (34%)	80 (34.2%)	18 (29.5%)
Clinical laboratory tests: AST (Female) (IU/L)*					
N	45 (7.3%)	none	PPD	PPD	none
< 2*ULNR	33 (73.3%)	none	PPD	PPD	none
≥2*ULNR	12 (26.7%)	none	PPD	PPD	none
Mean (SD)	29.2 (22.5)	-	28.3 (17.9)	30.4 (25.8)	-
Min-Max	10 - 118	-	15 - 67	13 - 85	-
Median [Q1-Q3]	19 [15 - 37]	-	22 [18 - 32]	17.5 [15.5 - 39.5]	-
Missing	568 (92.7%)	16 (100%)	42 (85.7%)	106 (93%)	29 (100%)
Clinical laboratory tests: AST (Male) (IU/L)*					
N	63 (9.1%)	PPD	PPD	PPD	PPD
< 2*ULNR	60 (95.2%)	PPD	PPD	PPD	PPD
≥2*ULNR	3 (4.8%)	none	PPD	PPD	none
Mean (SD)	26.3 (13)	30 (24)	28.5 (13.7)	20.7 (10.5)	18 (n/a)
Min-Max	7 - 74	13 - 47	7 - 47	7 - 37	18 - 18
Median [Q1-Q3]	23 [17 - 34]	30 [13 - 47]	27 [24 - 39]	17 [16 - 28]	18 [18 - 18]
Missing	628 (90.9%)	24 (92.3%)	45 (88.2%)	111 (92.5%)	31 (96.9%)
Clinical laboratory tests: ALT (Female) (IU/L)*					
N	391 (63.8%)	PPD	34 (69.4%)	76 (66.7%)	21 (72.4%)
< 2*ULNR	377 (96.4%)	PPD	29 (85.3%)	73 (96.1%)	21 (100%)
≥2*ULNR	14 (3.6%)	1 (16.7%)	5 (14.7%)	3 (3.9%)	-
Mean (SD)	28.6 (15.6)	24 (11.4)	33.9 (16.7)	29.9 (16.6)	18.7 (7)
Min-Max	7 - 91	13 - 39	11 - 79	7 - 91	9 - 31

	UK All patients (N=1,304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
Median [Q1-Q3]	25 [17 - 35]	22 [13 - 35]	31 [18 - 45]	25 [17.5 - 37]	16 [13 - 26]
Missing	222 (36.2%)	10 (62.5%)	15 (30.6%)	38 (33.3%)	8 (27.6%)
Clinical laboratory tests: ALT (Male) (IU/L)*					
N	426 (61.6%)	16 (61.5%)	40 (78.4%)	76 (63.3%)	23 (71.9%)
< 2*ULNR	PPD	16 (100%)	PPD	PPD	23 (100%)
≥2*ULNR	PPD	none	PPD		none
Mean (SD)	34.5 (18.9)	30.5 (19.5)	39.8 (17.1)	33.1 (15.3)	25.1 (12)
Min-Max	5 - 125	6 - 73	11 - 82	6 - 83	6 - 55
Median [Q1-Q3]	30 [22 - 42]	21.5 [18 - 39]	39 [28 - 50]	32 [22.5 - 40]	24 [18 - 32]
Missing	265 (38.4%)	10 (38.5%)	11 (21.6%)	44 (36.7%)	9 (28.1%)

* Derived variable
AST: aspartate amino transferase; ALT: alanine amino transferase; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HDL: high density lipoprotein; LDL: low density lipoprotein; SD: standard deviation; UACR: urine albumin/creatinine ratio; UK: United Kingdom
For computation of Missing patients, n/N=number of missing patients/total population, n/a=not applicable to report SD as N=1
'–' (dash) represents data which are not available from a site, and, therefore, cannot be calculated
Source: Interim Statistical Dataset UK, Table T_06

10.2.4. Other concomitant medications

10.2.4.1. By populations of interest

10.2.4.1.1. France

Details of other concomitant medications for the overall population in France are presented in Annex 3. All dulaglutide initiators with pre-existing severe renal failure, heart failure, severe GI disease, and elderly patients (aged ≥75 years) were prescribed other concomitant medications.

The three most common other concomitant medications included other ADMs (99.9%), lipid modifying drugs (98.9%), and vasodilator drugs acting on the renin-angiotensin system (98.8%). All patients across the subgroups were prescribed other ADMs. Lipid-modifying drugs and vasodilators acting on the renin-angiotensin system were other commonly prescribed concomitant medications across subgroups of interest (heart failure: 100%, severe GI disease: 100%, elderly patients: 99.2%; each).

10.2.4.1.2. Germany

Details of other concomitant medications for the overall population in Germany are presented in Annex 3. A majority of dulaglutide initiators with severe GI disease (93.5%), heart failure (91.5%), hepatic disease (90.1%), severe renal failure (73.1%), and patients aged ≥75 (84.7%) were prescribed other concomitant medications.

The three most common other concomitant medications included vasodilators acting on the renin-angiotensin system (37.8%), which were prescribed to a majority of patients with pre-

existing heart failure (57.1%), hepatic disease (48.3%), severe GI disease (55.2%), and among elderly patients (44.2%).

10.2.4.1.3. Spain

Details of other concomitant medications for the overall population in Spain are presented in Annex 3. More than 99% of dulaglutide initiators with pre-existing severe renal failure, heart failure, severe GI disease, hepatic disease, and elderly patients (aged ≥75 years) were prescribed other concomitant medications.

The three most common other concomitant medications included analgesics (69.4%), followed by antibacterials for systemic use (65.2%), and anti-inflammatory and anti-rheumatic products (56.3%). Analgesics were prescribed to most of the patients across all subgroups (hepatic disease: 75.8%, severe GI disease: 74.9%, elderly patients: 74.6%, heart failure: 74.2%, and severe renal failure: 72.2%). Antibacterials for systemic use were also commonly prescribed to patients with severe GI disease (73.9%), heart failure (71.9%), hepatic disease (68.1%), and elderly patients (70%); however, more patients with a history of severe renal failure (55.6%) were prescribed diuretics.

10.2.4.1.4. Sweden

Details of other concomitant medications for the overall population in Sweden are presented in Annex 3. Other concomitant medicationsMore than 99% of dulaglutide initiators with pre-existing severe renal failure, heart failure, severe GI disease, hepatic disease, and elderly patients (aged ≥75 years) were prescribed other concomitant medications.

The three most common other concomitant medications included lipid-modifying agents (69.9%) followed by vasodilators acting on the renin-angiotensin system (69.2%), and beta blocking agents (41.5%). Vasodilators acting on the renin-angiotensin system were prescribed to most of the patients across all subgroups (heart failure: 89.3%, elderly patients: 77.9%, severe GI disease: 71.1%, and hepatic disease: 60.2%). Lipid-modifying agents were more commonly prescribed to elderly patients aged ≥75 years (75.2%), patients with histories of severe GI disease (68.8%), and hepatic disease (43.7%). Beta blocking agents were more commonly prescribed to patients with pre-existing heart failure (85.5%).

10.2.4.1.5. UK

Details of other concomitant medications for the overall population in the UK are presented in Annex 3. More than half of dulaglutide initiators in the UK were prescribed other concomitant medications across subgroups (heart failure: 61.9%, elderly patients: 55.7%, severe GI disease: 51.7%, and hepatic disease: 51%).

The three most common other concomitant medications included lipid-modifying agents (72.2%) followed by vasodilators acting on the renin-angiotensin system (61.8%), and calcium channel blockers (27.1%). Lipid modifying agents were prescribed to most of dulaglutide initiators with pre-existing heart failure (83.3%), severe GI disease (71.8%), and hepatic disease (69.0%). Approximately 66% of dulaglutide initiators aged ≥75 years concomitantly were prescribed vasodilators acting on the renin-angiotensin system.

10.3. Outcomes data

This study is a cross-sectional drug utilisation study with no outcome data to analyse or report.

10.4. Main Results

Refer to results summarised in Section 10.2

10.5. Adverse Events/Adverse Reactions

Not applicable, as the study was carried out through secondary use of anonymised data already collected from the EHR databases and registries.

According to the current guidelines of the International Society for Pharmacoepidemiology (ISPE) (2007, Section VI) [12] and the EMA Guideline on Good Pharmacovigilance Practices (GVP): Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA, 2013, Section VI: C.1.2.1) [13], non-interventional studies which are based on secondary use of data do not require reporting of adverse events and adverse drug reactions.

11. Discussion

11.1. Key Results

The dulaglutide utilisation study objective was to describe dulaglutide use in real-world clinical prescribing conditions by demographic and clinical characteristics in overall dulaglutide initiators and in the following populations of interest: patients with severe renal failure, hepatic disease, heart failure, and severe GI disease; as well as in children and adolescents, elderly patients (≥75 years old), and pregnant and breast-feeding women. In addition, to describe medication errors (defined as prescribing dulaglutide to patients with T2DM in >1 weekly dose) and off-label use (defined as prescribing dulaglutide to patients without a diagnosis of T2DM, or prescribing dulaglutide as first-line therapy to patients with T2DM) overall and among populations of interest.

This final report describes patient characteristics and utilisation patterns of dulaglutide in five European countries (France, Germany, Spain, Sweden, and the UK).

11.1.1. Patient Characteristics and Utilisation Patterns

Between January 2015 and December 2017, a total of 15,619 dulaglutide initiators were eligible for analysis, corresponding to 5,456 in Sweden, 4,759 in Germany; 2,716 in Spain; 1,384 in France; and 1,304 in the UK. All dulaglutide initiators in Germany and the UK, and between 95 to 99% of those in France, Spain and Sweden were diagnosed with T2DM. A higher proportion of dulaglutide initiators in studied European countries were male and between the ages of 45 to 64 years.

The populations of interest are not mutually exclusive, where a patient could be part of more than one group, e.g. a dulaglutide initiator with heart failure history could be an elderly patient. Overall, no children or adolescents were identified among initiators of dulaglutide in Germany, Spain, and the UK, although PPD each from France and Sweden was an adolescent between the ages of 15 to 17 years. Slightly over one-third of dulaglutide initiators were elderly patients (≥65 years of age); those aged ≥75 years comprised 10.2%, 9.7%, 9.6%, 7.8%, and 4.7% in Germany, Sweden, France, Spain, and the UK, respectively. Among women treated with dulaglutide, PPD women in Germany, and PPD women each in Spain, Sweden, and the UK were pregnant, but none were breast-feeding at the time of starting treatment with dulaglutide.

Less than 1.5% of patients had pre-existing severe renal failure across the five countries, corresponding to 0.5% in Germany, 0.5% in Sweden, 1.3% in Spain, PPD in the UK, and none in France had pre-existing severe renal failure. The frequency of pre-existing hepatic disease among patients treated with dulaglutide was 16.6% in Spain, 7.7% in the UK, 3.2% in Germany, 1.9% in Sweden, and PPD in France. The most frequently reported hepatic disease in Spain was non-alcoholic fatty liver disease. It is in line with previously published literature on this disease in the SIDIAP database, where the estimated prevalence of non-alcoholic fatty liver disease was reported to be 25%, which was associated with male gender, age, metabolic syndrome and insulin resistance, among other factors [14]. The observed differences in the distribution of patients with hepatic disease in part reflect the heterogeneity of clinical practice and coding of

the condition of interest between study countries. Patients with a history of heart failure accounted for 10.6% of dulaglutide initiators in Germany, 7.2% in Sweden, 6.6% in Spain, 3.2% in the UK, and 1.5% in France. Patients with severe GI disease accounted for a small proportion of dulaglutide users, corresponding to 17.9% in the UK, 10.6% in Spain, 8.6% in Sweden, 8.1% in Germany, and 4.9% in France.

The present data show that between 95% and 100% of dulaglutide initiators were diagnosed with T2DM at the time of treatment initiation (Germany: 100.0%, the UK: 100%, Sweden: 98.5%, Spain: 98.4%, and France: 95.2%), with the vast majority being previously treated with other ADMs (Sweden: 97.1%, the UK: 87.1%, Spain: 84.9%, Germany: 82.8%, and France: 77.7%) including at the time of treatment with dulaglutide (France: 94.4%, Sweden: 91.7%, Spain: 75.8%, the UK: 75.5%, and Germany: 47.1%). This could reflect prescribing dulaglutide according to the label for T2DM, and as an add-on therapy rather than first-line T2DM therapy.

The average prescribed weekly dose of dulaglutide ranged between 0.8-1.4 across study countries, corresponding to 1.4 mg/week in Spain, 1.3 mg/week in Germany, Sweden, and the UK each, and 0.8 mg/week in France. Furthermore, the average weekly dose of dulaglutide is consistent with what is expected in T2DM patients given their duration of diabetes; for example in France, the 0.8 mg/week dose is expected in recently diagnosed T2DM patients (e.g., mean diabetes duration of 4 years with all patients having ≤10 years of T2DM duration), while the 1.4 mg/week dose is expected in those with longer duration of the disease (e.g., mean diabetes duration of almost 10 years in Spain with about 49% of the patients having >10 years of T2DM duration).

Up to 5% of dulaglutide initiators were prescribed dulaglutide in >1 weekly dose , with the exception of the UK where it was reported for 84.3% of patients. This high reported value can be attributed to administrative overlaps in the source data. In the UK, patients are permitted to collect prescriptions from the pharmacy every three months (refills) without having to see a prescriber for a new prescription [15]. This leads to administrative overlaps in prescriptions that could bias the calculations of dosage frequency, e.g. average weekly dose. Unlike other databases in the study, these medication overlaps are common in the UK CPRD [16-17]; therefore, the prevalence of prescribing dulaglutide in >1 weekly dose in the UK should be interpreted with caution.

More than 60% of patients who started treatment with dulaglutide had pre-existing hypertension and dyslipidaemia. Macrovascular complications, with ischaemic heart disease making up the largest proportion, was also observed as a common comorbidity in patients (67% to 83%) across all countries, except for patients in Spain who accounted for 19%. Conversely, microvascular complications were less prevalent overall. The distribution of these complications, however, varied across countries. Overall, between 1-3% of dulaglutide initiators had histories for solid tumours, with 0.5 to 1.4% affecting the breast.

Biguanides were the most widely prescribed concomitant ADMs in Sweden (75%), the UK (63%), and France (53%); whereas insulins were the most widely prescribed concomitant ADMs in Germany (53%) and Spain (35%). Similarly, at index date of dulaglutide initiation, biguanides were the most widely prescribed concurrent ADMs in France (76%), Sweden (61%), the UK (53%), and Spain (40.0%); however, insulins were the most widely prescribed at index date

among dulaglutide initiators in Germany (28%), and about 51% of patients in France received prescriptions for sulfonylureas at the time of dulaglutide start.

Clinical laboratory test results for dulaglutide initiators were documented in all countries except Sweden. Among the countries with available laboratory test results, a majority of dulaglutide initiators were reported to have HbA1c >7.5%, eGFR ≥30 mL/min/1.73 m^2, and serum creatinine <100 µmol/L during the 6-month baseline period before dulaglutide initiation. Urine albumin/creatinine ratio (UACR) was documented only in patients from Spain and the UK with most of the patients having UACR <30 mg/before starting treatment with dulaglutide. The majority of patients across countries had a history of LDL cholesterol <1.6 g/L, with Spain accounting for 89% of their population, whereas HDL cholesterol values were ≥0.35 g/L in most of the patients with France accounting for about 82%. The baseline mean LDL and HDL cholesterol measurements were highest in patients from Spain (2.6 g/L and 0.9 g/L, respectively). Across countries, more than 91% of dulaglutide initiators had baseline AST and ALT values of <2*ULNR. The mean baseline AST and ALT levels were highest among dulaglutide initiators in Germany (AST - females: 37.4 IU/L and males: 41.3 IU/L; ALT - females: 47.4 IU/L and males: 56.9 IU/L).

Between 56% and 100% of dulaglutide initiators were prescribed concomitant medications. The distribution of types of concomitant medications varied across the five countries. Lipid-modifying agents were frequently prescribed in patients from France (98.9%), the UK (72.2%), and Sweden (69.9%); whereas, vasodilators acting on the renin-angiotensin system were commonly prescribed across all countries except Spain, where a high proportion of patients were prescribed analgesics (69.4%), followed by systemic antibacterials (65.2%), and anti-inflammatory and anti-rheumatic drugs (56.3%).

11.2. Limitations

The main limitations were related to the lack of availability of some information in the databases that were used to address the study objectives:

- Data reported in the French and German-DA were collected through GPs. Nevertheless, a proportion of dulaglutide prescriptions were initiated by specialists and renewed by the GP. Some patients treated with dulaglutide were followed-up only by a specialist and would not be present in DA databases. Consequently, the number of patients initiated dulaglutide could be lower than expected in these databases.
- Some data elements were not routinely reported by the physicians (it depended on physicians' willingness and the usefulness of the information for clinical practice).
- The identification of disease severity was limited in the databases; it is necessary to define diagnosis via ICD-10 codes (DA, registry data).
- Pregnancy (via ICD-10) information was very limited in the French and German-DA.
- Data about breast-feeding were very limited in the databases in all countries.
- Apart from duration of diabetes, the SIDIAP database did not include information about diabetes history.
- Information on laboratory results were not available for Sweden. French and German-DA only had laboratory results available on a small proportion of their patient populations.

- In EHR databases, actual dispensing and administration of prescribed medications are not available, which adds a level of uncertainty to the dates of exposure to study drugs [18].
- In the UK, patients are permitted to collect prescriptions from the pharmacy every three months (refills) without having to see a clinician for a new prescription. This leads to administrative overlaps in prescriptions that could bias the calculations of dosage frequency, e.g. average weekly dose. Unlike other databases in the study, these medication prescription overlaps are common in the UK CPRD [16-17].

Other sources of selection bias, misclassification bias, and information bias related to databases are discussed below:

- **Selection Bias**
  For some databases, such as French and German-DA, the sample of GPs is representative of the physicians in each country in terms of the stratification factors used to select the panel. However, it is not known that the prescription pattern of physicians who belong to the panel was the same as that of physicians who are not part of the panel, especially those who were invited to take part but refused. Similar considerations can be expressed for physicians who belong for a long time and physicians recently included in the panel. To control this selection bias, the distribution of the strata in each database was compared to the distribution of strata of the corresponding physicians' population in the country.

- **Misclassification bias**
  If the study subjects were not categorised correctly with regards to exposure or selected patient characteristics, this would result in misclassification bias. Since, in this study, fully anonymised databases were used, it is, therefore, impossible to verify the information with source data. Hence, this bias is expected to persist across all study periods as it cannot be controlled as there is no possibility to check the information in the databases.

- **Information bias**
  In EHR databases, recording bias can result if the information is not systematically recorded. The information is recorded mainly when clinically useful. Consequently, the missing information is not always randomly missing. For example, clinicians tend to register abnormal values more often than normal ones. This is an inherent limitation of the EHR databases with the voluntary recording of information, as opposed to claims databases [18]. In this study, the extent of this bias is however, likely to be minimal, as the data which are collected is clinically important for the management of the diabetic patient.

11.3. Interpretation

This final report of the dulaglutide utilisation study suggests that dulaglutide is prescribed for the intended population for the treatment of T2DM in France, Germany, Spain, Sweden, and the UK; and dulaglutide initiators were comprised of a low proportion of patients with severe renal failure; hepatic disease; heart failure; severe gastrointestinal disease; children and adolescents; elderly patients; or pregnant or breast-feeding women. The trend of dulaglutide utilisation is consistent with what was observed in the first and second interim reports.

The differences in the distribution of subgroups of interest by countries, in part, reflect the variability in clinical practices, including diagnosis and treatment guidelines for the underlying conditions of interest, e.g. heart failure. Also, the broad definitions for some of these conditions, e.g. hepatic disease and severe GI disease, carry the potential for misclassification during variable measurement and analysis, e.g. hepato-biliary disorders might be coded as GI conditions in some countries. Moreover, the heterogeneous sources of these disparate databases contribute, in part, to the observed variability in study outcomes.

Additionally, the observed high prevalence of prescribing dulaglutide in >1 weekly dose in the UK should be interpreted with caution, which could be over-estimated due to measurement and misclassification biases that are attributed by prescribing and dispensing practices in the UK [15-17].

11.4. Generalisability

The selected electronic health records databases (IQVIA DA, SIDIAP, NPR and CPDR) for this study are designed to be representative for the selected countries (France, Germany, Spain, Sweden, and UK). In France, the database included only GPs, whereas in Germany the main prescribing specialties were GPs (general medicine and internal medicine) with diabetologist inclusive. In Spain, the main prescribing specialties (endocrinologists) were considered in addition to GPs.

No further restrictions regarding demographic characteristics, insurance status, comorbidities, region, or other, which could affect the external validity of results, were applied. Taking the known limitations of the databases into consideration, the findings of dulaglutide utilisation patterns in the target countries are generalisable to patients who started treatment with dulaglutide in France, Germany, Spain, Sweden, and UK.

12. Other information

Not applicable.

13. Conclusion

This final study report provides insights into the utilisation of dulaglutide among populations of interest in five European countries, which suggests that dulaglutide initiators included a low proportion of patients with severe renal failure; hepatic disease; heart failure; severe gastrointestinal disease; children and adolescents; elderly patients; or pregnant or breast-feeding women. Dulaglutide is generally being prescribed to the intended population according to the labelled indication in France, Germany, Spain, Sweden, and the UK.

14. References

1. Vilsbøll T, Agersø H, Krarup T, Holst JJ. Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects. J Clin Endocrinol Metab. 2003;88:220-4.
2. Tran KL, Park YI, Pandya S, Muliyil NJ, Jensen BD, Huynh K, et al. Overview of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Patients with Type 2 Diabetes. Am Health Drug Benefits. 2017;10(4):178-88.
3. Brice KR, Tzefos MK. The Clinical Efficacy and Safety of Glucagon-Like Peptide-1 (GLP-1) Agonists in Adults with Type 2 Diabetes Mellitus. Clin Med Insights Endocrinol Diabetes 2011;4:13-24.
4. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technol Assess 2010;14(36):1-248.
5. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. Diabetes Care. 2011;34:S279-84.
6. Kalra S, Baruah MP, Sahay RK, Unnikrishnan AG, Uppal S, Adetunji O. Glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes: Past, present, and future. Indian J Endocrinol Metab. 2016;20(2):254-67.
7. Jimenez-Solem E, Rasmussen MH, Christensen M, Knop FK. Dulaglutide, a long-acting GLP-1 analog fused with an Fc antibody fragment for the potential treatment of type 2 diabetes. Curr Opin Mol Ther. 2010;12(6):790-7.
8. EMA. Trulicity: EPAR - Summary for the public 2014. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002825/human_med_001821.jsp&mid=WC0b01ac058001d124.
9. Hepler CD, Segal R. Preventing Medication Errors and Improving Drug Therapy Outcomes: A Management System Approach. CRC Press Boca Raton, FL. 2003.
10. Becher H, Kostev K, Schroeder-Bernhardi D. Validity and representativeness of the "Disease Analyzer" patient database for use on pharmacoepidemiological and pharmacoeconomics studies. Int J Pharmacol Ther. 2009;47:617-26.
11. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011;11:450.
12. Pharmacoepidemiology ISf. Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology. 2015 03 June 2015.
13. EMA. Guideline on good pharmacovigilance practices (GVP), Module VI – management and reporting of adverse reactions to medicinal products, EMA 873138/2011. 2013.
14. Caballeria L, Pera G, Auladell MA, Toran P, Munoz L, Miranda D, et al. Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. European journal of gastroenterology & hepatology. 2010;22(1):24-32.
15. Harding M. General prescribing guidance. Patient. June 2019. Available from: https://patient.info/doctor/general-prescribing-guidance.

16 Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-836.

17 Doble B, Payne R, Harshfield A, Wilson ECF. Retrospective, multicohort analysis of the Clinical Practice Research Datalink (CPRD) to determine differences in the cost of medication wastage, dispensing fees and prescriber time of issuing either short (<60 days) or long (≥60 days) prescriptions lengths in primary care for common, chronic conditions in the UK. BMJ Open. 2017;7(12):e019382

18 Nordstrom BL, Fraeman KH, Lambrelli D. Electronic medical records. In: Ali AK, Hartzema AG, Editors. Post-Authorization Safety Studies of Medicinal Products. The PASS Book. Academic Press, Elsevier, Inc. 2018.

Annex 1. List of standalone documents

None.

Annex 2. Additional information

Not applicable.

Annex 3. Other concomitant medications

a. Description of other concomitant medications in France

ATC Therapeutic Group	France All patients (N=1384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
ANY OTHER CONCOMITANT MEDICATION	1384 (100.0%)	21 (100.0%)	68 (100.0%)	133 (100.0%)
A01 - PREPARATIONS STOMATOLOGIQUES, PREPARATIONS BUCCALES, DENTIFR	394 (28.5%)	PPD	14 (20.6%)	33 (24.8%)
A02 - ANTIACIDES, ANTIFLATULENTS ET ANTI-ULCEREUX	1341 (96.9%)	21 (100.0%)	66 (97.1%)	132 (99.2%)
A03 - MEDICAMENTS POUR LES TROUBLES GASTRO-INTESTINAUX FONCTIONNEL	1011 (73.0%)	14 (66.7%)	48 (70.6%)	96 (72.2%)
A04 - ANTIEMETIQUES ET ANTINAUSEEUX	357 (25.8%)	PPD	14 (20.6%)	23 (17.3%)
A05 - MEDICAMENTS CHOLAGOGUES ET HEPATOPROTECTEURS	129 (9.3%)	PPD		14 (10.5%)
A06 - LAXATIFS	799 (57.7%)	PPD	29 (42.6%)	79 (59.4%)
A07 - ANTIDIARRHEIQUES, SOLUTION ORALE ELECTROLYTES, ANTIINFLAMMAT	970 (70.1%)	PPD	48 (70.6%)	96 (72.2%)
A09 - MEDICAMENTS DE LA DIGESTION, ENZYMES DIGESTIVES INCLUSES	41 (3.0%)	0 (0.0%)	PPD	
A10 - MEDICAMENTS DU DIABETE	1383 (99.9%)	21 (100.0%)	68 (100.0%)	133 (100.0%)
A11 - VITAMINES	1154 (83.4%)	16 (76.2%)	49 (72.1%)	111 (83.5%)
A12 - SUPPLEMENTATION MINERALE	749 (54.1%)	13 (61.9%)	34 (50.0%)	84 (63.2%)
B01 - AGENTS ANTITHROMBOTIQUES	1311 (94.7%)	21 (100.0%)	64 (94.1%)	131 (98.5%)

ATC Therapeutic Group	France All patients (N=1384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
B02 - ANTIFIBRINOLYTIQUE, ANTIDOTE ANTICOAG., INHIBITEURS, COAG.SA	80 (5.8%)	PPD		
B03 - PREPARATIONS ANTI-ANEMIQUES	631 (45.6%)	PPD	24 (35.3%)	65 (48.9%)
C01 - MEDICAMENTS CARDIAQUES	781 (56.4%)	13 (61.9%)	30 (44.1%)	93 (69.9%)
C02 - ANTIHYPERTENSEURS	829 (59.9%)	13 (61.9%)	43 (63.2%)	76 (57.1%)
C03 - DIURETIQUES	1126 (81.4%)	19 (90.5%)	50 (73.5%)	110 (82.7%)
C04 - VASODILATATEURS CEREBRAUX ET PERIPHERIQUES	118 (8.5%)	PPD		15 (11.3%)
C05 - PREPARATIONS ANTIVARICOSIQUES, ANTIHEMORROIDAIRES	382 (27.6%)	PPD	15 (22.1%)	37 (27.8%)
C07 - BETABLOQUANTS	1262 (91.2%)	21 (100.0%)	57 (83.8%)	122 (91.7%)
C08 - ANTAGONISTES CALCIQUES	1170 (84.5%)	15 (71.4%)	50 (73.5%)	113 (85.0%)
C09 - MEDICAMENTS AGISSSANT SUR LE SYSTEME RENINE-ANGIOTENSINE	1367 (98.8%)	21 (100.0%)	68 (100.0%)	132 (99.2%)
C10 - REGULATEURS DU METABOLISME LIPIDIQUE ET MEDICAMENTS ANTI-ATH	1369 (98.9%)	21 (100.0%)	68 (100.0%)	132 (99.2%)
C11 - ASSOCIATIONS EN THERAPEUTIQUE CARDIOVASCULAIRE	88 (6.4%)	0 (0.0%)	PPD	
D01 - ANTIFONGIQUES, A USAGE DERMATOLOGIQUE	961 (69.4%)	14 (66.7%)	40 (58.8%)	88 (66.2%)
D02 - EMOLLIENTS, PROTECTEURS	706 (51.0%)	12 (57.1%)	25 (36.8%)	67 (50.4%)
D03 - AGENTS CICATRISANTS DES PLAIES	312 (22.5%)	PPD		31 (23.3%)
D05 - PRODUITS NON STERIODIENS POUR LES DESORDRES INFLAMMATOIRES D	187 (13.5%)	PPD		15 (11.3%)

ATC Therapeutic Group	France All patients (N=1384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
D06 - ANTIBIOTIQUES, SULFAMIDES ET ANTIVIRAUX A USAGE TOPIQUE	693 (50.1%)	PPD	26 (38.2%)	68 (51.1%)
D07 - CORTICOIDES A USAGE TOPIQUE	872 (63.0%)	PPD	39 (57.4%)	83 (62.4%)
D08 - ANTISEPTIQUES ET DESINFECTANTS	853 (61.6%)	14 (66.7%)	32 (47.1%)	80 (60.2%)
D10 - PREPARATIONS ANTI-ACNEIQUES	76 (5.5%)	0 (0.0%)	PPD	
D11 - AUTRES PREPARATIONS DERMATOLOGIQUES	51 (3.7%)	PPD		
G01 - ANTI-INFECTIEUX GYNECOLOGIQUES	232 (16.8%)	PPD		30 (22.6%)
G02 - AUTRES MEDICAMENTS GYNECOLOGIQUES	184 (13.3%)	0 (0.0%)	PPD	19 (14.3%)
G03 - HORMONES SEXUELLES ET PRODUITS D'EFFET SIMILAIRE, ACTION SYS	487 (35.2%)	PPD	18 (26.5%)	51 (38.3%)
G04 - MEDICAMENTS UROLOGIQUES	940 (67.9%)	15 (71.4%)	40 (58.8%)	95 (71.4%)
H02 - CORTICOSTEROIDES A USAGE SYSTEMIQUE	659 (47.6%)	PPD	25 (36.8%)	60 (45.1%)
H03 - MEDICAMENTS DE LA THYROIDE	1032 (74.6%)	14 (66.7%)	41 (60.3%)	98 (73.7%)
H04 - AUTRES HORMONES	104 (7.5%)	PPD		13 (9.8%)
J01 - ANTIBACTERIENS SYSTEMIQUES	1216 (87.9%)	19 (90.5%)	51 (75.0%)	118 (88.7%)
J02 - AGENTS SYSTEMIQUES POUR INFECTIONS FONGIQUES	248 (17.9%)	PPD	12 (17.6%)	19 (14.3%)
J05 - ANTIVIRAUX A USAGE SYSTEMIQUE	216 (15.6%)	PPD		23 (17.3%)
J07 - VACCINS	183 (13.2%)	PPD		19 (14.3%)
K01 - SOLUTIONS INTRAVEINEUSES	23 (1.7%)	0 (0.0%)	PPD	
K04 - SOLUTIONS INJECTABLES < 100ML	39 (2.8%)	PPD		

ATC Therapeutic Group	France All patients (N=1384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
K05 - SOLUTIONS D'IRRIGATION	21 (1.5%)	0 (0.0%)	0 (0.0%)	PPD
L01 - ANTINEOPLASIQUES	18 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
L02 - THERAPIE PAR HORMONE CYTOSTATIQUE	202 (14.6%)	PPD		23 (17.3%)
L04 - IMMUNOSUPPRESSEURS	55 (4.0%)	PPD		6 (4.5%)
M01 - ANTIINFLAMMATOIRES ET ANTIRHUMATISMAUX	1150 (83.1%)	14 (66.7%)	48 (70.6%)	105 (78.9%)
M02 - ANTIRHUMATISMAUX TOPIQUES	1129 (81.6%)	17 (81.0%)	49 (72.1%)	111 (83.5%)
M03 - MYORELAXANTS	597 (43.1%)	PPD	26 (38.2%)	54 (40.6%)
M04 - MEDICAMENTS ANTIGOUTTEUX	1029 (74.3%)	18 (85.7%)	46 (67.6%)	101 (75.9%)
M05 - AUTRES MEDICAMENTS DES DESORDRES MUSCULAIRES ET DU SQUELETTE	449 (32.4%)	PPD	18 (26.5%)	48 (36.1%)
N01 - ANESTHESIQUES	186 (13.4%)	PPD		20 (15.0%)
N02 - ANALGESIQUES	1346 (97.3%)	20 (95.2%)	65 (95.6%)	129 (97.0%)
N03 - ANTIEPILEPTIQUES	843 (60.9%)	12 (57.1%)	35 (51.5%)	85 (63.9%)
N04 - ANTIPARKINSONIENS	190 (13.7%)	PPD		14 (10.5%)
N05 - PSYCHOLEPTIQUES	1215 (87.8%)	18 (85.7%)	51 (75.0%)	124 (93.2%)
N06 - PSYCHOANALEPTIQUES, MEDICAMENTS ANTI-OBESITE EXCLUS	1114 (80.5%)	17 (81.0%)	53 (77.9%)	118 (88.7%)
N07 - AUTRES MEDICAMENTS DU SNC	426 (30.8%)	PPD	16 (23.5%)	34 (25.6%)
P01 - ANTIPROTOZOAIRES ET ANTHELMINTHIQUES	109 (7.9%)	PPD		
P03 - ANTIPARASITAIRES EXTERNES, INCLUANT SCABICIDES, INSECTICIDES	59 (4.3%)	PPD		
R01 - PREPARATIONS NASALES	1054 (76.2%)	13 (61.9%)	47 (69.1%)	107 (80.5%)
R02 - MEDICAMENTS POUR LA GORGE	453 (32.7%)	PPD	17 (25.0%)	46 (34.6%)
R03 - ANTIASTHMATIQUES ET MEDICAMENTS DE LA BPCO	1178 (85.1%)	18 (85.7%)	51 (75.0%)	110 (82.7%)

ATC Therapeutic Group	France All patients (N=1384)	Heart failure (N=21)	Severe GI disease (N=68)	Aged ≥75 (N=133)
R04 - PRODUITS DE FRICTION THORACIQUE ET AUTRES PRODUITS A INHALER	139 (10.0%)	PPD		
R05 - MEDICAMENTS DU RHUME ET DE LA TOUX	1208 (87.3%)	15 (71.4%)	52 (76.5%)	120 (90.2%)
R06 - ANTIHISTAMINIQUES SYSTEMIQUES	1073 (77.5%)	12 (57.1%)	46 (67.6%)	99 (74.4%)
S01 - PRODUITS OPHTALMOLOGIQUES	800 (57.8%)	PPD	33 (48.5%)	73 (54.9%)
S02 - MEDICAMENTS OTOLOGIQUES	412 (29.8%)	PPD	17 (25.0%)	42 (31.6%)
T02 - TESTS DIAGNOSTIQUES	1306 (94.4%)	20 (95.2%)	61 (89.7%)	129 (97.0%)
T03 - EQUIPEMENT ET ACCESSOIRES DE DIAGNOSTIC	33 (2.4%)	0 (0.0%)	PPD	
V03 - AUTRES PRODUITS THERAPEUTIQUES	168 (12.1%)	PPD		16 (12.0%)
V06 - PRODUITS DIETETIQUES	44 (3.2%)	PPD	0 (0.0%)	PPD
V07 - AUTRES PRODUITS NON THERAPEUTIQUES	565 (40.8%)	PPD	22 (32.4%)	51 (38.3%)
V99 - AUTRES PRESCRIPTIONS	1334 (96.4%)	20 (95.2%)	63 (92.6%)	128 (96.2%)

* Data are reported only in French and are not available in English language
ATC: Anatomical Therapeutic Chemical classification
Subgroup of patients with hepatic disease has not been presented due to privacy morns (i.e. N<10)
Source: Interim Statistical Dataset France, Table T_07

b. Description of other concomitant medications in Germany

ATC Therapeutic Group	Germany All patients (N=4759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
ANY OTHER CONCOMITANT MEDICATION	3774 (79.3%)	19 (73.1%)	460 (91.5%)	136 (90.1%)	361 (93.5%)	410 (84.7%)
A01 - STOMATOLOGICALS	13 (0.3%)	0 (0.0%)	PPD	0 (0.0%)	PPD	PPD
A02 - A-ACID A-FLAT A-ULCERANTS	758 (15.9%)	PPD	168 (33.4%)	41 (27.2%)	123 (31.9%)	104 (21.5%)

ATC Therapeutic Group	Germany All patients (N=4759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
A03 - FUNCTL.GI DISORDER DRUG	82 (1.7%)	PPD	13 (2.6%)	PPD	19 (4.9%)	15 (3.1%)
A04 - ANTIEMETICS ANTINAUSEANTS	PPD	PPD	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
A05 - CHOLAGOG/HEPATIC PROTECT	PPD	PPD	PPD			
A06 - CONSTIPAT+BOWEL CLEANSER	53 (1.1%)	PPD	17 (3.4%)	PPD	14 (3.6%)	16 (3.3%)
A07 - A-DIAR ORAL ELEC+A-INFLAM	56 (1.2%)	0 (0.0%)	PPD	PPD	21 (5.4%)	PPD
A08 - ANTIOBESITY PREPARATIONS	PPD	0 (0.0%)	PPD	0 (0.0%)	PPD	0 (0.0%)
A09 - DIGESTIVES INCL ENZYMES	22 (0.5%)	0 (0.0%)	PPD	PPD		
A10 - DRUGS USED IN DIABETES	1354 (28.5%)	PPD	170 (33.8%)	51 (33.8%)	106 (27.5%)	153 (31.6%)
A11 - VITAMINS	151 (3.2%)	PPD	30 (6.0%)	10 (6.6%)	30 (7.8%)	34 (7.0%)
A12 - MINERAL SUPPLEMENTS	55 (1.2%)	PPD	15 (3.0%)	PPD		14 (2.9%)
A13 - TONICS	PPD	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
A16 - OTHER METABOLIC PRODUCTS	PPD		0 (0.0%)	0 (0.0%)	PPD	0 (0.0%)
B01 - ANTITHROMBOTIC AGENTS	739 (15.5%)	PPD	192 (38.2%)	32 (21.2%)	107 (27.7%)	138 (28.5%)
B02 - BLOOD COAG SYST OTH PROD	PPD	0 (0.0%)	PPD	0 (0.0%)	0 (0.0%)	PPD
B03 - ANTIANAEMICS	59 (1.2%)	0 (0.0%)	22 (4.4%)	PPD	14 (3.6%)	15 (3.1%)
C01 - CARDIAC THERAPY	192 (4.0%)	PPD	83 (16.5%)	PPD	26 (6.7%)	47 (9.7%)
C02 - ANTIHYPERTENSIVES	223 (4.7%)	PPD	54 (10.7%)	PPD	38 (9.8%)	38 (7.9%)
C03 - DIURETICS	735 (15.4%)	PPD	244 (48.5%)	38 (25.2%)	108 (28.0%)	141 (29.1%)

ATC Therapeutic Group	Germany All patients (N=4759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
C04 - CEREB/PERIPH.VASOTHERAPS	PPD		0 (0.0%)	PPD		
C05 - A-VARICOSE/A-HAEMOROID PR	12 (0.3%)	0 (0.0%)	PPD	0 (0.0%)	PPD	
C06 - OTH CARDIOVASCULAR PRDS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	PPD
C07 - BETA BLOCKING AGENTS	1211 (25.4%)	PPD	247 (49.1%)	52 (34.4%)	161 (41.7%)	164 (33.9%)
C08 - CALCIUM ANTAGONISTS	610 (12.8%)	PPD	116 (23.1%)	32 (21.2%)	84 (21.8%)	102 (21.1%)
C09 - AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	1799 (37.8%)	PPD	287 (57.1%)	73 (48.3%)	213 (55.2%)	214 (44.2%)
C10 - LIPID-REG/ANTI-ATHEROMA	1259 (26.5%)	PPD	215 (42.7%)	50 (33.1%)	141 (36.5%)	152 (31.4%)
C11 - C.V.MULTITHER.COMB.PRODS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	PPD	0 (0.0%)
D01 - ANTIFUNGALS DERMATOLOGICL	66 (1.4%)	0 (0.0%)	PPD	PPD		PPD
D02 - EMOLLIENTS & PROTECTIVES	PPD	0 (0.0%)	PPD	PPD	0 (0.0%)	0 (0.0%)
D03 - WOUND HEALING AGENTS	23 (0.5%)	0 (0.0%)	PPD	PPD)	PPD	
D04 - TOPICAL ANTIPRURITICS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
D05 - NON-STER PRD INFLAM SKIN	PPD	0 (0.0%)	PPD	PPD	0 (0.0%)	0 (0.0%)
D06 - TOP A-BACTS & A-VIRALS	17 (0.4%)	0 (0.0%)	PPD	PPD	PPD	0 (0.0%)
D07 - TOPICAL CORTICOSTEROIDS	149 (3.1%)	PPD	31 (6.2%)	PPD	20 (5.2%)	26 (5.4%)

ATC Therapeutic Group	Germany All patients (N=4759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
D08 - ANTISEPTICS+DISINFECTANTS	29 (0.6%)	0 (0.0%)	PPD	PPD	PPD	PPD
D10 - ANTI-ACNE PREPARATIONS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	PPD	
D11 - OTHER DERMATOLOGICAL PREP	PPD	PPD			0 (0.0%)	PPD
G01 - GYNAE ANTI-INFECTIVES	15 (0.3%)	0 (0.0%)	PPD	0 (0.0%)	PPD	
G02 - OTHER GYNAECOLOGICALS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	PPD
G03 - SEX HORMONES SYSTEM ONLY	31 (0.7%)	0 (0.0%)	PPD			0 (0.0%)
G04 - UROLOGICALS	196 (4.1%)	PPD	37 (7.4%)	PPD	40 (10.4%)	39 (8.1%)
H02 - SYSTEMIC CORTICOSTEROIDS	78 (1.6%)	PPD	16 (3.2%)	PPD	14 (3.6%)	19 (3.9%)
H03 - THYROID THERAPY	517 (10.9%)	3 (11.5%)	85 (16.9%)	20 (13.2%)	79 (20.5%)	58 (12.0%)
H04 - OTHER HORMONES	12 (0.3%)	0 (0.0%)	1PPD			
J01 - SYSTEMIC ANTIBACTERIALS	277 (5.8%)	PPD	43 (8.5%)	13 (8.6%)	43 (11.1%)	24 (5.0%)
J02 - SYST ANTIFUNGAL AGENTS	18 (0.4%)	PPD		0 (0.0%)	PPD	
J05 - ANTIVIRALS SYSTEMIC USE	PPD	0 (0.0%)	PPD			
J07 - VACCINES	25 (0.5%)	0 (0.0%)	PPD	0 (0.0%)	PPD	
K01 - INTRAVENOUS SOLUTIONS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	PPD	
K04 - INJ SOLN/INF ADDIT <100ML	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	PPD	0 (0.0%)
L02 - CYTOSATIC HORMONE THERAPY	PPD	0 (0.0%)	PPD			0 (0.0%)
L04 - IMMUNOSUPPRESSANTS	12 (0.3%)	PPD				0 (0.0%)

ATC Therapeutic Group	Germany All patients (N=4759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
M01 - ANTI-RHEUMATIC SYSTEM	397 (8.3%)	PPD	71 (14.1%)	27 (17.9%)	51 (13.2%)	37 (7.6%)
M02 - ANTIRHEUMATICS TOPICAL	31 (0.7%)	PPD				
M03 - MUSCLE RELAXANTS	26 (0.5%)	0 (0.0%)	PPD			
M04 - ANTI-GOUT PREPARATIONS	361 (7.6%)	PPD	103 (20.5%)	24 (15.9%)	55 (14.2%)	60 (12.4%)
M05 - OTHER MUSCULO-SKELETAL	26 (0.5%)	PPD				
N01 - ANAESTHETICS	PPD	0 (0.0%)	PPD	0 (0.0%)	PPD	
N02 - ANALGESICS	422 (8.9%)	PPD	102 (20.3%)	21 (13.9%)	66 (17.1%)	68 (14.0%)
N03 - ANTI-EPILEPTICS	203 (4.3%)	0 (0.0%)	52 (10.3%)	PPD	28 (7.3%)	36 (7.4%)
N04 - ANTI-PARKINSON PREPS	48 (1.0%)	PPD	12 (2.4%)	PPD	PPD	PPD
N05 - PSYCHOLEPTICS	171 (3.6%)	PPD	37 (7.4%)	PPD	23 (6.0%)	38 (7.9%)
N06 - PSYCHOANALEPTICS	254 (5.3%)	PPD	53 (10.5%)	19 (12.6%)	41 (10.6%)	35 (7.2%)
N07 - OTHER CNS DRUGS	33 (0.7%)	PPD	PPD	PPD	PPD	19 (3.9%)
P01 - ANTIPROTOZ.& ANTHELMINT	PPD	0 (0.0%)	PPD	PPD	0 (0.0%)	0 (0.0%)
P03 - ECTOPARASITICIDES	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
R01 - NASAL PREPARATIONS	54 (1.1%)	0 (0.0%)	PPD		12 (3.1%)	PPD
R02 - PHARYNGEAL PREPARATIONS	25 (0.5%)	0 (0.0%)	PPD			0 (0.0%)
R03 - ANTI-ASTHMA & COPD PROD	253 (5.3%)	PPD	70 (13.9%)	PPD	39 (10.1%)	45 (9.3%)
R04 - CHEST RUBS & INHALANTS	PPD	0 (0.0%)	PPD	0 (0.0%)	0 (0.0%)	PPD

ATC Therapeutic Group	Germany All patients (N=4759)	Severe renal failure (N=26)	Heart failure (N=503)	Hepatic disease (N=151)	Severe GI disease (N=386)	Aged ≥75 (N=484)
R05 - COUGH & COLD PREPARATIONS	147 (3.1%)	PPD	31 (6.2%)	PPD	26 (6.7%)	12 (2.5%)
R06 - ANTIHISTAMINES SYSTEMIC	40 (0.8%)	0 (0.0%)	PPD			
R07 - OTHER RESPIRATORY PREPS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
S01 - OPHTHALMOLOGICALS	52 (1.1%)	0 (0.0%)	PPD			
S02 - OTOLOGICALS	PPD			0 (0.0%)	PPD	
T02 - DIAGNOSTIC TESTS	1806 (37.9%)	12 (46.2%)	225 (44.7%)	69 (45.7%)	140 (36.3%)	203 (41.9%)
V03 - OTHER THERAPEUTIC PRODS	26 (0.5%)	0 (0.0%)	PPD	0 (0.0%)	PPD	
V06 - GENERAL NUTRIENTS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

ATC: Anatomical Therapeutic Chemical classification

Source: Interim Statistical Dataset Germany, Table T_07

c. Description of other concomitant medications in Spain

ATC Therapeutic Group	Spain All patients (N=2716)[#]	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
ANY OTHER CONCOMITANT MEDICATION	2692 (99.1%)	36 (100.0%)	178 (100.0%)	448 (99.3%)	286 (99.7%)	213 (100.0%)
A01 - STOMATOLOGICAL PREPARATIONS	31 (1.1%)	0 (0.0%)	PPD		)	3 3 (1.4%)
A02 - DRUGS FOR ACID RELATED DISORDERS	981 (36.1%)	12 (33.3%)	57 (32.0%)	173 (38.4%)	105 (36.6%)	79 (37.1%)
A03 - DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	423 (15.6%)	PPD	25 (14.0%)	93 (20.6%)	65 (22.6%)	27 (12.7%)
A04 - ANTIEMETICS AND ANTINAUSEANTS	23 (0.8%)	PPD				

ATC Therapeutic Group	Spain All patients (N=2716)[#]	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
A05 - BILE AND LIVER THERAPY	PPD	0 (0.0%)	PPD			0 (0.0%)
A06 - DRUGS FOR CONSTIPATION	105 (3.9%)	PPD	16 (9.0%)	21 (4.7%)	18 (6.3%)	16 (7.5%)
A07 - ANTIDIARRHEALS, INTESTINAL ANTI-INFLAMMATORY/ANTIINFECTIVE AGEN	209 (7.7%)	PPD	26 (14.6%)	40 (8.9%)	51 (17.8%)	24 (11.3%)
A08 - ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	PPD	0 (0.0%)	PPD			0 (0.0%)
A09 - DIGESTIVES, INCL. ENZYMES	PPD	0 (0.0%)	0 (0.0%)	PPD	0 (0.0%)	0 (0.0%)
A11 - VITAMINS	385 (14.2%)v	PPD	27 (15.2%)	72 (16.0%)	42 (14.6%)	39 (18.3%)
A12 - MINERAL SUPPLEMENTS	163 (6.0%)	PPD	27 (15.2%)	30 (6.7%)	22 (7.7%)	27 (12.7%)
A14 - ANABOLIC AGENTS FOR SYSTEMIC USE	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B01- ANTITHROMBOTIC AGENTS	793 (29.2%)	19 (52.8%)	90 (50.6%)	121 (26.8%)	95 (33.1%)	90 (42.3%)
B02 - ANTIHEMORRHAGICS	48 (1.8%)	PPD	PPD			
B03 - ANTIANEMIC PREPARATIONS	486 (17.9%)	17 (47.2%)	50 (28.1%)	80 (17.7%)	72 (25.1%)	68 (31.9%)
B05 - BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	29 (1.1%)	0 (0.0%)	PPD			
C01 - CARDIAC THERAPY	287 (10.6%)	PPD	60 (33.7%)	41 (9.1%)	35 (12.2%)	39 (18.3%)
C02 - ANTIHYPERTENSIVES	117 (4.3%)	PPD	13 (7.3%)	19 (4.2%)	12 (4.2%)	14 (6.6%)
C03 - DIURETICS	580 (21.4%)	20 (55.6%)	100 (56.2%)	108 (23.9%)	79 (27.5%)	74 (34.7%)
C04 - PERIPHERAL VASODILATORS	31 (1.1%)	PPD				
C05 - VASOPROTECTIVES	95 (3.5%)	0 (0.0%)	PPD	18 (4.0%)	PPD	
C07 - BETA BLOCKING AGENTS	369 (13.6%)	PPD	56 (31.5%)	64 (14.2%)	48 (16.7%)	52 (24.4%)

ATC Therapeutic Group	Spain All patients (N=2716)[#]	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
C08 - CALCIUM CHANNEL BLOCKERS	437 (16.1%)	14 (38.9%)	46 (25.8%)	71 (15.7%)	52 (18.1%)	54 (25.4%)
C09 - AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	968 (35.6%)	23 (63.9%)	84 (47.2%)	150 (33.3%)	104 (36.2%)	83 (39.0%)
C10 - LIPID MODIFYING AGENTS	1136 (41.8%)	19 (52.8%)	87 (48.9%)	192 (42.6%)	118 (41.1%)	82 (38.5%)
D01 - ANTIFUNGALS FOR DERMATOLOGICAL USE	682 (25.1%)	PPD	42 (23.6%)	118 (26.2%)	82 (28.6%)	51 (23.9%)
D02 - EMOLLIENTS AND PROTECTIVES	PPD	0 (0.0%)	0 (0.0%)	PPD		0 (0.0%)
D03 - PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	21 (0.8%)	0 (0.0%)	PPD			
D05 - ANTIPSORIATICS	51 (1.9%)	PPD				
D06 - ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	394 (14.5%)	PPD	27 (15.2%)	78 (17.3%)	53 (18.5%)	37 (17.4%)
D07 - CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	631 (23.2%)	PPD	41 (23.0%)	123 (27.3%)	82 (28.6%)	51 (23.9%)
D08 - ANTISEPTICS AND DIDINFECTANTS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
D09 - MEDICATED DRESSINGS	PPD	0 (0.0%)	PPD	0 (0.0%)	0 (0.0%)	PPD
D10 - ANTI-ACNE PREPARATIONS	22 (0.8%)	0 (0.0%)	PPD	PPD		
D11 - OTHER DERMATOLOGICAL PREPARATIONS	47 (1.7%)	0 (0.0%)	PPD	PPD		
G01 - GYNECOLOGICAL ANTI-INFECTIVES AND ANTISEPTICS	269 (9.9%)	PPD	13 (7.3%)	53 (11.8%)	36 (12.5%)	18 (8.5%)
G02 - OTHER GYNECOLOGICALS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

ATC Therapeutic Group	Spain All patients (N=2716)[#]	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
G03 - SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	77 (2.8%)	0 (0.0%)	PPD	15 (3.3%)	PPD	PPD
G04 - UROLOGICALS	287 (10.6%)	PPD	21 (11.8%)	43 (9.5%)	34 (11.8%)	26 (12.2%)
H01 - PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES	PPD	0 (0.0%)	PPD	0 (0.0%)	PPD	PPD
H02 - CORTICOSTEROIDS FOR SYSTEMIC USE	399 (14.7%)	PPD	46 (25.8%)	74 (16.4%)	54 (18.8%)	37 (17.4%)
H03 - THYROID THERAPY	115 (4.2%)	PPD		20 (4.4%)	12 (4.2%)	PPD
H04 - PANCREATIC HORMONES	355 (13.1%)	PPD	22 (12.4%)	53 (11.8%)	41 (14.3%)	33 (15.5%)
H05 - CALCIUM HOMEOSTASIS	PPD			0 (0.0%)	0 (0.0%)	PPD
J01 - ANTIBACTERIALS FOR SYSTEMIC USE	1770 (65.2%)	19 (52.8%)	128 (71.9%)	307 (68.1%)	212 (73.9%)	149 (70.0%)
J02 - ANTIMYCOTICS FOR SYSTEMIC USE	156 (5.7%)	PPD		41 (9.1%)	21 (7.3%)	PPD
J04 - ANTIMYCOBACTERIALS	PPD	0 (0.0%)	PPD			0 (0.0%)
J05 - ANTIVIRALS FOR SYSTEMIC USE	75 (2.8%)	PPD		16 (3.5%)	14 (4.9%)	14 (6.6%)
J07 - VACCINES	PPD	0 (0.0%)	PPD	0 (0.0%)	PPD	0 (0.0%)
L01 - ANTINEOPLASTIC AGENTS	PPD	0 (0.0%)	PPD	PPD		
L02 - ENDOCRINE THERAPY	22 (0.8%)	0 (0.0%)	PPD			
L04 - IMMUNOSUPPRESSANTS	28 (1.0%)	PPD				
M01 - ANTI-INFLAMMATORY AND ANTI-RHEUMATIC PRODUCTS	1530 (56.3%)	PPD	59 (33.1%)	294 (65.2%)	152 (53.0%)	97 (45.5%)
M02 - TOPICAL PRODUCTS FOR	49 (1.8%)	0 (0.0%)	PPD			

ATC Therapeutic Group	Spain All patients (N=2716)[#]	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
JOINT AND MUSCULAR PAIN						
M03 - MUSCLE RELAXANTS	189 (7.0%)	PPD		38 (8.4%)	19 (6.6%)	PPD
M04 - ANTI-GOUT PREPARATIONS	178 (6.6%)	PPD	34 (19.1%)	29 (6.4%)	24 (8.4%)	29 (13.6%)
M05 - DRUGS FOR TREATMENT OF BONE DISEASES	43 (1.6%)	PPD				
N01 - ANESTHETICS	184 (6.8%)	PPD	19 (10.7%)	43 (9.5%)	20 (7.0%)	22 (10.3%)
N02 - ANALGESICS	1885 (69.4%)	26 (72.2%)	132 (74.2%)	342 (75.8%)	215 (74.9%)	159 (74.6%)
N03 - ANTI-EPILEPTICS	493 (18.2%)	PPD	31 (17.4%)	91 (20.2%)	60 (20.9%)	39 (18.3%)
N04 - ANTI-PARKINSON DRUGS	31 (1.1%)	0 (0.0%)	PPD			
N05 - PSYCHOLEPTICS	932 (34.3%)	17 (47.2%)	70 (39.3%)	182 (40.4%)	115 (40.1%)	81 (38.0%)
N06 - PSYCHOANALEPTICS	668 (24.6%)	PPD	46 (25.8%)	129 (28.6%)	78 (27.2%)	44 (20.7%)
N07 - OTHER NERVOUS SYSTEM DRUGS	233 (8.6%)	PPD	18 (10.1%)	47 (10.4%)	38 (13.2%)	26 (12.2%)
P01 - ANTIPROTOZOALS	50 (1.8%)	PPD		13 (2.9%)	13 (4.5%)	PPD
P02 - ANTHELMINTICS	PPD	0 (0.0%)	PPD	PPD		
P03 - ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLEN	12 (0.4%)	PPD	0 (0.0%)	PPD	PPD	
R01 - NASAL PREPARATIONS	370 (13.6%)	PPD	25 (14.0%)	75 (16.6%)	51 (17.8%)	29 (13.6%)
R02 - THROAT PREPARATIONS	PPD		0 (0.0%)	PPD	0 (0.0%)	0 (0.0%)
R03 - DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	790 (29.1%)	14 (38.9%)	100 (56.2%)	154 (34.1%)	112 (39.0%)	79 (37.1%)
R05 - COUGH AND COLD PREPARATIONS	474 (17.5%)	PPD	44 (24.7%)	89 (19.7%)	59 (20.6%)	50 (23.5%)
R06 - ANTIHISTAMINES FOR SYSTEMIC USE	737 (27.1%)	PPD	45 (25.3%)	134 (29.7%)	84 (29.3%)	57 (26.8%)

ATC Therapeutic Group	Spain All patients (N=2716)[#]	Severe renal failure (N=36)	Heart failure (N=178)	Hepatic disease (N=451)	Severe GI disease (N=287)	Aged ≥75 (N=213)
S01 - OPHTHALMOLOGICALS	664 (24.4%)	10 (27.8%)	48 (27.0%)	115 (25.5%)	94 (32.8%)	90 (42.3%)
S02 - OTOLOGICALS	220 (8.1%)	PPD	12 (6.7%)	44 (9.8%)	27 (9.4%)	22 (10.3%)
S03 - OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS	PPD	0 (0.0%)	0 (0.0%)	PPD	0 (0.0%)	0 (0.0%)
V03 - ALL OTHER THERAPEUTIC PRODUCTS	21 (0.8%)	PPD				
V07 - ALL OTHER NON-THERAPEUTIC PRODUCTS	PPD	0 (0.0%)	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)

ATC: Anatomical Therapeutic Chemical classification

Source: Interim Statistical Dataset Spain, Table T_07

d. Description of other concomitant medications in Sweden

ATC Therapeutic Group	Sweden All patients (N=5456)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
ANY OTHER CONCOMITANT MEDICATION	5319 (97.5%)	392 (100.0%)	102 (99.0%)	468 (99.4%)	528 (99.8%)
B01 ANTITHROMBOTIC AGENTS	2060 (37.8%)	321 (81.9%)	32 (31.1%)	217 (46.1%)	361 (68.2%)
B02 ANTIHEMORRHAGICS	13 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B03 ANTIANEMIC PREPARATIONS	1195 (21.9%)	110 (28.1%)	23 (22.3%)	140 (29.7%)	166 (31.4%)
C01 CARDIAC THERAPY	500 (9.2%)	157 (40.1%)	12 (11.7%)	73 (15.5%)	115 (21.7%)
C02 ANTIHYPERTENSIVES	134 (2.5%)	17 (4.3%)	PPD		
C03 DIURETICS	1456 (26.7%)	302 (77.0%)	39 (37.9%)	151 (32.1%)	256 (48.4%)
C05 VASOPROTECTIVES	60 (1.1%)	PPD		12 (2.5%)	PPD
C07 BETA BLOCKING AGENTS	2264 (41.5%)	335 (85.5%)	38 (36.9%)	226 (48.0%)	312 (59.0%)

ATC Therapeutic Group	Sweden All patients (N=5456)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
C08 CALCIUM CHANNEL BLOCKERS	1816 (33.3%)	127 (32.4%)	17 (16.5%)	144 (30.6%)	205 (38.8%)
C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	3773 (69.2%)	350 (89.3%)	62 (60.2%)	335 (71.1%)	412 (77.9%)
C10 LIPID MODIFYING AGENTS	3815 (69.9%)	319 (81.4%)	45 (43.7%)	324 (68.8%)	398 (75.2%)
D01 ANTIFUNGALS FOR DERMATOLOGICAL USE	362 (6.6%)	41 (10.5%)	12 (11.7%)	53 (11.3%)	39 (7.4%)
D02 EMOLLIENTS AND PROTECTIVES	517 (9.5%)	70 (17.9%)	19 (18.4%)	64 (13.6%)	81 (15.3%)
D04 ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	PPD	0 (0.0%)	0 (0.0%)	PPD	
D05 ANTIPSORIATICS	64 (1.2%)	PPD			
D06 ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	48 (0.9%)	PPD	0 (0.0%)	PPD	
D07 CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	527 (9.7%)	55 (14.0%)	PPD	60 (12.7%)	61 (11.5%)
D08 ANTISEPTICS AND DISINFECTANTS	14 (0.3%)	PPD	0 (0.0%)	0 (0.0%)	PPD
D09 MEDICATED DRESSINGS	PPD		0 (0.0%)	PPD	
D10 ANTI-ACNE PREPARATIONS	15 (0.3%)	PPD	0 (0.0%)	PPD	
D11 OTHER DERMATOLOGICAL PREPARATIONS	24 (0.4%)	PPD	0 (0.0%)	PPD	
G01 GYNECOLOGICAL ANTI-INFECTIVES AND ANTISEPTICS	31 (0.6%)	PPD			
G02 OTHER GYNECOLOGICALS	19 (0.3%)	0 (0.0%)	0 (0.0%)	PPD	0 (0.0%)
G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	442 (8.1%)	22 (5.6%)	PPD	57 (12.1%)	36 (6.8%)

ATC Therapeutic Group	Sweden All patients (N=5456)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
G04 UROLOGICALS	770 (14.1%)	79 (20.2%)	15 (14.6%)	88 (18.7%)	107 (20.2%)
H01 PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES	16 (0.3%)	0 (0.0%)	PPD		0 (0.0%)
H02 CORTICOSTEROIDS FOR SYSTEMIC USE	364 (6.7%)	64 (16.3%)	PPD	64 (13.6%)	63 (11.9%)
H03 THYROID THERAPY	551 (10.1%)	38 (9.7%)	PPD	56 (11.9%)	78 (14.7%)
H04 PANCREATIC HORMONES	PPD	0 (0.0%)	0 (0.0%)	PPD	
H05 CALCIUM HOMEOSTASIS	PPD	0 (0.0%)	0 (0.0%)	PPD	-
J01 ANTIBACTERIALS FOR SYSTEMIC USE	1080 (19.8%)	133 (33.9%)	36 (35.0%)	122 (25.9%)	119 (22.5%)
J02 ANTIMYCOTICS FOR SYSTEMIC USE	195 (3.6%)	PPD		28 (5.9%)	PPD
J04 ANTIMYCOBACTERIALS	PPD	0 (0.0%)	0 (0.0%)	PPD	0 (0.0%)
J05 ANTIVIRALS FOR SYSTEMIC USE	62 (1.1%)	PPD			
J06 IMMUNE SERA AND IMMUNOGLOBULINS	PPD			0 (0.0%)	0 (0.0%)
J07 VACCINES	15 (0.3%)	PPD			0 (0.0%)
L01 ANTINEOPLASTIC AGENTS	PPD	0 (0.0%)	PPD		
L02 ENDOCRINE THERAPY	50 (0.9%)	PPD	0 (0.0%)	PPD	
L04 IMMUNOSUPPRESSANTS	138 (2.5%)	13 (3.3%)	PPD	25 (5.3%)	13 (2.5%)
M01 ANTI-INFLAMMATORY AND ANTI-RHEUMATIC PRODUCTS	919 (16.8%)	41 (10.5%)	20 (19.4%)	74 (15.7%)	45 (8.5%)
M02 TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	70 (1.3%)	PPD			14 (2.6%)
M03 MUSCLE RELAXANTS	133 (2.4%)	PPD		12 (2.5%)	PPD
M04 ANTI-GOUT PREPARATIONS	262 (4.8%)	57 (14.5%)	PPD	29 (6.2%)	48 (9.1%)
M05 DRUGS FOR TREATMENT OF BONE DISEASES	63 (1.2%)	PPD	PPD		15 (2.8%)

ATC Therapeutic Group	Sweden All patients (N=5456)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
M09 OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	PPD				
N01 ANESTHETICS	40 (0.7%)	PPD	0 (0.0%)	PPD	
N02 ANALGESICS	1924 (35.3%)	213 (54.3%)	48 (46.6%)	224 (47.6%)	253 (47.8%)
N03 ANTI-EPILEPTICS	351 (6.4%)	30 (7.7%)	17 (16.5%)	34 (7.2%)	26 (4.9%)
N04 ANTI-PARKINSON DRUGS	124 (2.3%)	17 (4.3%)	PPD	19 (4.0%)	15 (2.8%)
N05 PSYCHOLEPTICS	1140 (20.9%)	109 (27.8%)	41 (39.8%)	136 (28.9%)	154 (29.1%)
N06 PSYCHOANALEPTICS	1109 (20.3%)	86 (21.9%)	25 (24.3%)	124 (26.3%)	110 (20.8%)
N07 OTHER NERVOUS SYSTEM DRUGS	82 (1.5%)	PPD			
P01 ANTIPROTOZOALS	51 (0.9%)	PPD			
P02 ANTHELMINTICS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P03 ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLE	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
R01 NASAL PREPARATIONS	467 (8.6%)	36 (9.2%)	PPD	51 (10.8%)	38 (7.2%)
R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	786 (14.4%)	99 (25.3%)	22 (21.4%)	91 (19.3%)	103 (19.5%)
R05 COUGH AND COLD PREPARATIONS	526 (9.6%)	65 (16.6%)	6 (5.8%)	57 (12.1%)	72 (13.6%)
R06 ANTIHISTAMINES FOR SYSTEMIC USE	617 (11.3%)	43 (11.0%)	20 (19.4%)	82 (17.4%)	38 (7.2%)
S01 OPHTHALMOLOGICALS	555 (10.2%)	54 (13.8%)	11 (10.7%)	49 (10.4%)	104 (19.7%)
S02 OTOLOGICALS	37 (0.7%)	PPD	0 (0.0%)	PPD	
S03 OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS	124 (2.3%)	PPD	PPD		16 (3.0%)
V01 ALLERGENS	PPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
V03 ALL OTHER THERAPEUTIC PRODUCTS	PPD				

ATC Therapeutic Group	Sweden All patients (N=5456)	Heart failure (N=392)	Hepatic disease (N=103)	Severe GI disease (N=471)	Aged ≥75 (N=529)
V07 ALL OTHER NON-THERAPEUTIC PRODUCTS	PPD		0 (0.0%)	PPD	

ATC: Anatomical Therapeutic Chemical classification

Source: Interim Statistical Dataset Sweden, Table T_07

e. Description of other concomitant medications in UK

ATC Therapeutic Group	UK All patients (N=1304)	Heart failure (N=42)	Hepatic disease (N=100)	Severe GI disease (N=234)	Aged ≥75 (N=61)
ANY OTHER CONCOMITANT MEDICATION	724 (55.5%)	26 (61.9%)	51 (51.0%)	121 (51.7%)	34 (55.7%)
C01 - CARDIAC THERAPY	53 (4.1%)	PPD		13 (5.6%)	PPD
C02 - ANTIHYPERTENSIVES	93 (7.1%)	PPD		21 (9.0%)	PPD
C03 - DIURETICS	309 (23.7%)	30 (71.4%)	29 (29.0%)	56 (23.9%)	25 (41.0%)
C04 - PERIPHERAL VASODILATORS	PPD	0 (0.0%)	0 (0.0%)	PPD	0 (0.0%)
C07 - BETA BLOCKING AGENTS	282 (21.6%)	31 (73.8%)	17 (17.0%)	61 (26.1%)	22 (36.1%)
C08 - CALCIUM CHANNEL BLOCKERS	354 (27.1%)	12 (28.6%)	25 (25.0%)	64 (27.4%)	18 (29.5%)
C09 - AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	806 (61.8%)	30 (71.4%)	58 (58.0%)	140 (59.8%)	40 (65.6%)
C10 - LIPID MODIFYING AGENTS	942 (72.2%)	35 (83.3%)	69 (69.0%)	168 (71.8%)	39 (63.9%)

ATC: Anatomical Therapeutic Chemical classification

Source: Interim Statistical Dataset UK, Table T_07