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| **Intrinsic factors examined** |  |  |
| **Age (Adults/Paediatric)** | Review | No separate dose/dosing regimen is recommended in any patient  subgroups sub groups due to intrinsic (age, sex, race, ethnicity, body weight, renal  impairment, hepatic impairment) and extrinsic factors (9, 11,15)  The exposure-response relationship  for HbA1c was similar in males and females and across subgroups of body weight, BMI, age, race,  ethnicity, renal function and upper GI disease (86)  Oral Semaglutide has not been studied in paediatric patients (3.2.2.7.3 pg 23) |
| Label | Safety and efficacy of RYBELSUS have not been established in pediatric patients (younger than 18 years). (10,13)  No overall differences in safety or efficacy were detected between these patients and younger patients, but  greater sensitivity of some older individuals cannot be ruled out. (10) |
| **Gender (Male/Female)** | Review | Population PK analysis did not identify age, body weight, gender, ethnicity and race to have any clinically  relevant impact on the pharmacokinetics of oral semaglutide (9,11,23) |
| Label | Based on a population pharmacokinetic analysis, age, sex, race, ethnicity, upper GI disease, and renal  impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide (13,15) |
| **Body weight/weight cutoffs if any** | Review | PopPK analysis did not identify age, body weight, gender, ethnicity and race to have any clinically  relevant impact on the pharmacokinetics of oral semaglutide (9,11,15, 23) |
| Label | The exposure of  semaglutide decreases with an increase in body weight. However, RYBELSUS doses of 7 mg and 14 mg  provide adequate systemic exposure over the body weight range of 40-188 kg evaluated in the clinical trials.(13) |
| **Race** | Review | PopPK analysis did not identify age, body weight, gender, ethnicity and race to have any clinically  relevant impact on the pharmacokinetics of oral semaglutide (9,11,23) |
| Label | Based on a population pharmacokinetic analysis, age, sex, race, ethnicity, upper GI disease, and renal  impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide (13) |
| **Height** | Review | No data found |
| Label | No data found |
| **Organ dysfunction/Renal** | Review | No separate dose/dosing regimen is recommended in any patient  subgroups sub groups due to intrinsic (age, sex, race, ethnicity, body weight, renal  impairment, hepatic impairment) and extrinsic factors (9, 11) |
| Label | No dose adjustment of RYBELSUS is recommended for patients with renal impairment evaluated in a 26-week clinical study that included 324 patients  with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m2  ). (10) |
| **Organ dysfunction/Hepatic** | Review | No separate dose/dosing regimen is recommended in any patient  subgroups sub groups due to intrinsic (age, sex, race, ethnicity, body weight, renal  impairment, hepatic impairment) and extrinsic factors (9, 11) |
| Label | No dose adjustment of RYBELSUS is recommended for patients with hepatic impairment in a study in subjects with different degrees of hepatic impairment (10) |
| **Clinical Pharmacology contribution in dose modification/dose escalation in adults/Paediatric population?** | Review | Dose adjustment of oral Semaglutide is not required for patients based on age (3.3.4 pg 34) |
| Label | Safety and efficacy of RYBELSUS have not been established in paediatric patients (younger than 18 years). (10)  No overall differences in safety or efficacy were detected between these patients and younger patients, but  greater sensitivity of some older individuals cannot be ruled out. (10) |
| **Clinical Pharmacology contribution in dose modification/dose escalation among male/female population?** | Review | No separate dose/dosing regimen is recommended in any patient  based on sex.  With increasing semaglutide exposure, a larger HbA1c change from baseline was seen in subjects with  higher baseline HbA1c, and in subjects with shorter diabetes duration. The exposure-response relationship  for HbA1c was similar in males and females (9, 86) |
| Label | Based on a population pharmacokinetic analysis, age, sex, race, ethnicity, upper GI disease, and renal  impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide (13) |
| **Clinical Pharmacology contribution in dose modification/dose escalation in various body weights/BMI?** | Review | A dose-response relationship with an ED50 value of approximately 15 mg was observed for  change in body weight after 26 weeks of treatment with oral semaglutide. The steepest part of the curve  ranged up to 20 mg, after which the effects started to plateau (31)  Patients with body weights  less than 70 kg had approximately twice the exposure of patients with body weight less than 110 kg.  After considering the large variability in PK and shape of the exposure-response curve, dose-adjustment  for weight is not necessary (66) |
| Label | The exposure of  semaglutide decreases with an increase in body weight. However, RYBELSUS doses of 7 mg and 14 mg  provide adequate systemic exposure over the body weight range of 40-188 kg evaluated in the clinical trials. (13) |
| **Clinical Pharmacology contribution in dose modification/dose escalation among different races?** | Review | Race and ethnicity do not appear to affect the PK of oral Semaglutide and SNAC among Japanese and Caucasian subjects (pg 40,41).  Moreover, 90% Clearance of drug was relative in white Asians and black African American subjects in a population PK analysis in Phase 3 trials (pg 43) |
| Label | Based on a population pharmacokinetic analysis, age, sex, race, ethnicity, upper GI disease, and renal  impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide (13) |
| **Clinical Pharmacology contribution in dose modification/dose escalation among different heights?** | Review | No such data was found |
| Label | No such data was found |
| **Clinical Pharmacology contribution in dose modification/dose escalation in renal dysfunction?** | Review | Semaglutide exposure (SNAC also) did not exhibit any consistent patterns of increase or decrease with increasing renal  Impairment evaluated in a multi-center, open-label,  multiple-dose, parallel group study (Trial 4079) in which systemic exposure of semaglutide in subjects  with mild, moderate, severe renal impairment and end stage renal disease (ESRD) was compared with  that in subjects with normal renal function following a 10 day dosing regimen of oral semaglutide – 5 mg  for 5 days followed by 10 mg for 5 days. (pg 22, 34,37).  Although exposure of SNAC metabolites increased with  increasing degree of renal impairment, amounting up to 26-fold increase in metabolite E1246 exposure,  this does not seem to pose any safety concern considering the safety margin established with non-clinical  studies (37) |
| Label | Monitor  renal function when initiating or escalating doses of RYBELSUS in patients reporting severe adverse  gastrointestinal reactions (5)  No dose adjustment of RYBELSUS is recommended for patients with renal impairment evaluated in a 26-week clinical study that included 324 patients  with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m2  ). (10) |
| **Clinical Pharmacology contribution in dose modification/dose escalation in hepatic dysfunction?** | Review | Following 10 days of once daily dosing of oral semaglutide, the exposure of semaglutide (AUC and Cmax)  were similar across the 4 hepatic function groups, indicating that semaglutide exposure is not affected by  the degree of hepatic function conducted an open-label, multiple dose, parallel group trial to investigate the PK properties  of semaglutide and SNAC in subjects with impaired hepatic function to assess whether there was a need  to adjust the dose of oral semaglutide in subjects with hepatic impairment compared to subjects with  normal hepatic function (36, )  Following 10 days of once daily dosing of oral semaglutide in the abovementioned clinical trial, the exposure of SNAC (AUC and Cmax)  increased with a decrease in hepatic function (36) |
| Label | No dose adjustment of RYBELSUS is recommended for patients with hepatic impairment in a study in subjects with different degrees of hepatic impairment (10) |
| **Clinical Pharmacology contribution in dose modification/dose escalation in other body organs?** | Review | Following 10 days of once daily dosing of oral semaglutide (and SNAC), there was no statistically significant  difference in exposure of semaglutide between subjects with and  without upper GI disease, however the exposure of semaglutide appeared to be slightly higher in subjects  with upper GI disease compared to subjects without upper GI disease evaluated through an open-label, multiple doses, parallel group trial to investigate the PK, safety  and tolerability of semaglutide and SNAC in T2DM subjects with upper GI disease compared to subjects  without upper GI disease (39, 40) |
| Label | The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation receiving RYBELSUS 7 mg (4%) and RYBELSUS 14 mg (8%) discontinued treatment due to gastrointestinal  adverse reactions than patients receiving placebo (6) |
| **Does Clinical Pharmacology provide any contribution in optimal dosing conditions/therapeutic individualization?** | Review | The results from the clinical pharmacology studies and two clinical studies (trials 3794 and 3957),  support a recommended use for oral semaglutide tablet to be taken on an empty stomach and be  swallowed whole with up to half a glass of water equivalent to 120 mL without splitting, crushing  or chewing the tablet. After taking oral semaglutide, patients are recommended to wait at least 30  minutes before the first meal or drink of the day and taking other oral medications (8,9,10,16)  Semaglutide dosing should  follow a titration scheme. Taking two 7 mg semaglutide tablets to achieve a 14 mg dose is not  recommended. Patients treated with weekly 0.5 mg OZEMPIC (semaglutide) subcutaneous injection can  be transitioned to 14 mg oral semaglutide by starting oral therapy 2 to -4 days following the last injection. There is no equivalent dose of oral semaglutide for 1 mg OZEMPIC  injection (11,26) |
|  | Label | Instruct patients to take RYBELSUS at least 30 minutes before the first food, beverage, or other oral  medications of the day with no more than 4 ounces of plain water only  Waiting less than 30 minutes, or taking RYBELSUS with food, beverages (other than plain water) or other  oral medications will lessen the effect of RYBELSUS by decreasing its absorption. Waiting more than 30  minutes to eat may increase the absorption of RYBELSUS (1,3,11) |
| **Clinical pharmacology contribution in providing DDI/Drug-food interaction** | Review | Effect of food on the PK of semaglutide was studied in a single-center, randomized, open-labeled,  multiple-dose, parallel group study in healthy subjects (n=78). Subjects were randomized 1:1:1 to three  treatment arms (fed, fasting and reference). All subjects received 5 mg oral semaglutide for 5 days  followed by 10 mg oral semaglutide for 5 days. Subjects in the fed group fasted for 10 hours overnight  after which they received a high-fat, high-calorie meal followed by administration of semaglutide with  240 mL of water and 4-hour post-dose fasting period. Subjects in the fasting group fasted 10-hour  overnight followed by administration of semaglutide with 240 mL water and a 4-hour post-dose fasting  period. In the reference group, subjects fasted 6-hour overnight followed by administration of  semaglutide with 120 mL water and 30 min post-dose fasting. As a result of the low semaglutide exposure  in the fed group, patients are advised to take oral semaglutide on an empty stomach (43)  Semaglutide causes a delay of gastric emptying and thereby has the potential to impact the absorption of  other oral medications. In DDI trials, semaglutide did not affect the absorption of orally administered medications to any  clinically relevant degree. Therefore, no dose adjustment is required. When a single dose of levothyroxine 600 ug was concurrently  administered with semaglutide, the total exposure (AUC) of thyroxine (adjusted for endogenous levels)  was increased by 33%. (46,48,49). |
|  | Label | The risk of hypoglycemia is increased when RYBELSUS is used in combination with insulin secretagogues  (e.g., sulfonylureas) or insulin. The risk of hypoglycemia may be lowered by a reduction in the dose of  sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin  RYBELSUS causes a delay of gastric emptying, and thereby has the potential to impact the absorption of other  oral medications. Levothyroxine exposure was increased 33% (90% CI: 125-142) when administered with  RYBELSUS in a drug interaction study.  Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic  index or that require clinical monitoring (8)  The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered  oral medicinal products. Trials were conducted to study the potential effect of semaglutide on the absorption of  oral medications taken with semaglutide administered orally at steady-state exposure.  No clinically relevant drug-drug interaction with semaglutide (13) |
| **Clinical Pharmacology contribution in preliminary labelling concepts in final packing inserts** | Review | Recommended dosage: Taking two 7 mg TRADENAME (Rybelsus) tablets to achieve a 14 mg dose is not  Recommended (12)  Pharmacology and clinical PK (10,3.2.2 pg 16, 17,18) |
|  | Label |  |
| **Clinical pharmacology information provides supportive evidence of**  **effectiveness** | Review | The data presented in this NDA provides supportive evidence of effectiveness for oral  semaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2  diabetes mellitus. Semaglutide exposures following oral administration were comparable to the  exposure range observed following subcutaneous administration (27). |
|  | Label |  |
| **Does clinical pharmacology provide any evidence of warnings/precautions?** | Review | Oral semaglutide is not recommended as a first-line therapy for patients who have inadequate glycemic  control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans  Oral semaglutide has not been studied in patients with a history of pancreatitis. Other antidiabetic therapies  should be considered in patients with a history of pancreatitis  Oral semaglutide is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of  patients with diabetic ketoacidosis, as it would not be effective in these settings (30,31) |
|  | Label | RYBELSUS is not recommended as a first-line therapy for patients who have inadequate glycemic control  on diet and exercise.  RYBELSUS has not been studied in patients with a history of pancreatitis  RYBELSUS is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients  with diabetic ketoacidosis, as it would not be effective in these settings (Limitations of Use 1,3,5)  Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the  postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship  between MTC and GLP-1 receptor agonist use in humans (1,4)  The absolute risk  increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy  at baseline. Moreover, the effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been  studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic  retinopathy (5) |
| **Does clinical pharmacology provide evidence of drug use in specific population?** | Review | No data available |
|  | Label | Available data with RYBELSUS use in pregnant women are insufficient to evaluate for a drug-associated risk  of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are clinical considerations  regarding the risks of poorly controlled diabetes in pregnancy. Poorly controlled diabetes during pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. (8,9)  There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the  effects on milk production. (9)  Discontinue RYBELSUS in women at least 2 months before a planned pregnancy due to the long washout  period for semaglutide (10) |