Renal safety profile of Stribild

In clinical studies and post-marketing safety surveillance for tenofovir disoproxil fumarate, rare events of renal failure, renal impairment, and proximal tubulopathy (including Fanconi syndrome) have been reported. In some patients proximal renal tubulopathy has been associated with myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures), rhabdomyolysis, muscle weakness, hypokalaemia and hypophosphataemia.

In the clinical studies of Stribild over 144 weeks, 13 (1.9%) subjects in the Stribild group (n=701) and 8 (2.3%) subjects in the ritonavir-boosted atazanavir plus emtricitabine/tenofovir disoproxil group (n=355) discontinued study drug due to a renal adverse reaction. Of these discontinuations, 7 in the Stribild group and 1 in the ATV/r+ FTC/TDF group occurred during the first 48 weeks. Four (0.6%) of the subjects who received Stribild developed laboratory findings consistent with proximal tubulopathy leading to discontinuation of Stribild during the first 48 weeks. No additional proximal renal tubular dysfunction cases were reported from week 48 to week 144. Two of the 4 subjects had renal impairment (i.e. creatinine clearance less than 70 mL/min) at baseline. The laboratory findings in these 4 subjects with evidence of proximal renal tubular dysfunction cases were reported from week 48 to week 144.

Stribild should be discontinued in patients with confirmed creatinine clearance that falls to <70 mL/min while on treatment unless it is considered that the potential benefit of this combination of antiretroviral agents for the individual patient outweighs the risks of continuing with therapy.

Monitoring of renal function

The recommendations for monitoring renal function in all patients prior to and during Stribild therapy are provided in Table 1 below.

Patients who experience a confirmed increase in serum creatinine of greater than 26.5 µmol/L (0.3 mg/dL) from baseline should be closely monitored for renal safety.

Patients who have previously discontinued treatment with tenofovir disoproxil fumarate due to renal toxicity should not be treated with Stribild.

There is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products such as Stribild.

Important points to consider

- Patients who have previously discontinued treatment with tenofovir disoproxil fumarate due to renal toxicity should not be treated with Stribild.
- Check all patients' creatinine clearance, urine glucose and urine protein before starting Stribild therapy.
- Stribild should not be initiated in patients with creatinine clearance below 70 mL/min.
- During Stribild therapy, creatinine clearance, serum phosphate, urine glucose and urine protein should be assessed regularly (every 4 weeks during the 1st year and then every 3 months) (see Table 1 see overleaf).
- A more frequent monitoring of renal function in patients at risk for renal impairment is required.
- Closely monitor for renal safety in patients who experience a confirmed increase in serum creatinine of greater than 26.5 µmol/L (0.3 mg/dL) from baseline.
- Re-evaluate renal function within 1 week if serum phosphate is <0.48 mmol/L (1.5 mg/dL) or creatinine clearance decreases to <70 mL/min during Stribild therapy.
- Discontinue Stribild therapy in patients with a confirmed creatinine clearance <50 mL/min or with decreases in serum phosphate to <0.32 mmol/L (1.0 mg/dL).
- Interrupting treatment with Stribild should also be considered in case of progressive decline of renal function when no other cause has been identified.
- Avoid concurrent or recent use of nephrotoxic medicinal products.

Stribild is a single tablet regimen containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as fumarate) that is indicated for the treatment of human immunodeficiency virus 1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment-naive or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild.

Specific recommendations for use of Stribild are detailed below.

Patients who experience a confirmed increase in serum creatinine of greater than 26.5 µmol/L (0.3 mg/dL) from baseline should be closely monitored for renal safety.

If serum phosphate is <0.48 mmol/L (1.5 mg/dL) or creatinine clearance is decreased to <70 mL/min in any patient receiving Stribild, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. It is recommended that Stribild is discontinued in patients with confirmed creatinine clearance that falls to <70 mL/min while on treatment unless it is considered that the potential benefit of this combination of antiretroviral agents for the individual patient outweighs the risks of continuing with therapy.

Stribild should be discontinued in patients with confirmed creatinine clearance that falls to <50 mL/min or with decreases in serum phosphate to <0.32 mmol/L (1.0 mg/dL).

Interrupting treatment with Stribild should also be considered in case of progressive decline of renal function when no other cause has been identified.

Table 1: Monitoring of renal function

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Parameter</th>
<th>Prior to Stribild</th>
<th>During 1st year on Stribild*</th>
<th>&gt;1 year on Stribild*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Creatinine clearance, urine glucose and urine protein</td>
<td>At baseline</td>
<td>Every 4 weeks</td>
<td>Every 3 months</td>
</tr>
</tbody>
</table>

Table 1: Monitoring of renal function

* In patients at risk for renal impairment, a more frequent monitoring of renal function is required.
STRI-BL® PRESCRIBING INFORMATION
Presentation: Stribild film-coated tablet. Each film-coated tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 150 mg of emtricitabine, and 245 mg of tenofovir disoproxil fumarate equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir aš fumurate.

Indications: Treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 16 years and older who are antiretroviral treatment-naive or are infected with HIV-1 for whom a combination of two antiretroviral agents is required. Stribild is contraindicated in patients with confirmed resistance to all three antiretroviral agents in Stribild.

Dosage & Administration: Adults. One tablet once daily in combination with a nucleoside reverse transcriptase inhibitor (NRTI) unless otherwise instructed by the healthcare professional.

Patients who experience a confirmed increase in serum creatinine concentration should be re-evaluated within one week. It is recommended that renal function should be monitored weekly. If Stribild is co-administered with a non-steroidal anti-inflammatory drug (NSAID), renal function should be monitored adequately. Renal failure, renal impairment, elevated creatinine, hyperphosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate.

Interactions: Any interactions identified with Stribild’s components should be considered.

Stribild should not be initiated in patients with GFR ≤ 70 mL/min. Close monitoring of renal function when no other cause has been identified is recommended. Stribild should be discontinued in patients with confirmed GFR < 50 mL/min by calculated creatinine clearance (CCr) that falls to ≤ 50 mL/min (CCr ≥ 50 mL/min is not considered). If serum creatinine is ≥ 1.5 mg/dL (133 µmol/L), Stribild should be discontinued.

In patients with severe hepatic impairment (Child-Pugh class C), dose reduction below 70 mL/min. It should be discontinued.

Caution: Safety and efficacy have not been established. Stribild should be initiated in patients over the age of 65 years and be monitored closely.

Co-administration of Stribild with drugs that inhibit CYP3A and/or BCRP, OATP1B1 and OATP1B3 may result in increased plasma concentrations of Stribild, which may result in loss of therapeutic effect and development of resistance. Co-administration of Stribild and nephrotoxic agents is unavoidable, renal function should be discontinued.

In patients with a confirmed increase in serum creatinine concentration, Stribild should be discontinued in patients with confirmed resistance to all three antiretroviral agents in Stribild.

Stribild should be used during pregnancy only if the potential benefit justifies the potential risk. It should not be used during breastfeeding.

For Healthcare Professionals prescribing in the United Kingdom

Adverse events should be reported. Reporting forms and information can be found by accessing the website www.hpra.ie or by telephone +353 1 6764971.

For Healthcare Professionals prescribing in the Republic of Ireland

Suspected adverse reactions should be reported to the HPRA Pharmacovigilance using reporting forms and information can be found by accessing the website www.hpra.ie or by telephone +353 1 6764971.

A summary of the product characteristics can be found by accessing the website www.hpra.ie or by telephone +353 1 6764971.

Drug Interactions: Interactions identified with Stribild’s components should be considered.

Metabolism: Stribild film-coated tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 150 mg of emtricitabine, and 245 mg of tenofovir disoproxil fumarate equivalent to 300 mg of tenofovir aš fumurate.

References:
1. Stribild Summary of Product Characteristics
2. Date of Preparation: January 2015

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