Saxagliptin (BMS-477118, Onglyza) Datasheet

Technical Data

<table>
<thead>
<tr>
<th>Molecular Weight (MW)</th>
<th>315.41</th>
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<tbody>
<tr>
<td>CAS No.</td>
<td>361442-04-8, 709031-78-7 (HCl), 361442-05-9 (TFA)</td>
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<tr>
<td>Synonyms</td>
<td>N/A</td>
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Biological Activity

Description: Saxagliptin (BMS-477118, Onglyza) is a selective and reversible DPP4 inhibitor with IC50 of 26 nM.

Targets: DPP4

IC50: 26 nM

In vitro: Saxagliptin has an inhibition constant Ki of 1.3 nM for DPP4 inhibition, which is 10-fold more potent than either vildagliptin or sitagliptin (another two DPP4 inhibitors) with Ki of 13 and 18 nM, respectively. In addition, Saxagliptin demonstrates greater specificity for DPP4 than for either the DPP8 or DPP9 enzymes (400- and 75-fold, respectively). The main metabolic activity of saxagliptin is two-fold less potent than the parent. Both Saxagliptin and its metabolite are highly selective (>4000-fold) for the prevention of DPP4 compared with a range of other proteases (selectivity of sitagliptin and vildagliptin for DPP4 is >2600 and <250-fold, respectively, compared with DPP8 and DPP9). Saxagliptin may reduce the degradation of the incretin hormone glucagon-like peptide-1, thereby enhancing its actions, and is associated with improved β-cell function and suppression of glucagon secretion.

In vivo: Maximal responses of saxagliptin in glucose excursion in Zucker fa/fa rats are associated with plasma DPP4 inhibition of approximately 60% vs. control, and no additional antihyperglycemic effects are seen at higher percent inhibition. Saxagliptin is highly effective at eliciting marked dose-dependent enhancements in glucose clearance in the dose range 0.13-1.3 mg/kg in ob/ob mice relative to controls. Saxagliptin dose-dependently elevates plasma insulin significantly at 15 min post-oGTT, with coconcurrent improvement in glucose clearance cures at 60 min post-oGTT.

Clinical Trials

Features

Protocol (Only for Reference)

In vitro DPP4 inhibition assays: Inhibition of human DPP4 activity is measured under steady-state conditions by following the absorbance increase at 405 nm upon the cleavage of the pseudosubstrate, Gly-Pro-pNA. Assays are performed in 96-well plates using a Thermomax plate reader. Typically reactions contained 100 μL of ATE buffer (100 mM Aces, 52 mM Tris, 52 mM ethanoamine, pH 7.4), 0.45 mM enzyme, either 120 or 100 μM of substrate (S < Kᵢ) and S > Kᵢ, Km = 180 μM and variable concentration of the inhibitor. To ensure steady-state conditions for slow-binding inhibitors, enzyme is preincubated with saxagliptin for 40 min prior to substrate addition. All serial inhibitor dilutions are in DMSO and final solvent concentration did not exceed 1%. Inhibitor potency is evaluated by fitting inhibition data to IC50 (1 + (S/Kᵢ))

References


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