Sitagliptin

Sitagliptin, sold under the brand name **Januvia** among others, is an anti-diabetic medication used to treat type 2 diabetes.[2] In the United Kingdom it is listed as less preferred than metformin or a sulfonylurea.[3] It is taken by mouth.[2] It is also available in the fixed-dose combination medication sitagliptin/metformin (Janumet, Janumet XR).[2]

Common side effects include headaches, swelling of the legs, and upper respiratory tract infections.[2] Serious side effects may include angioedema, low blood sugar, kidney problems, pancreatitis, and joint pain.[2] Whether use in pregnancy or breastfeeding is safe is unclear.[4] It is in the dipeptidyl peptidase-4 (DPP-4) inhibitor class and works by increasing the production of insulin and decreasing the production of glucagon by the pancreas.[2]

Sitagliptin was developed by Merck & Co. and approved for medical use in the United States in 2006.[2] In 2018, it was the 83rd most commonly prescribed medication in the United States, with more than 9 million prescriptions.[5][6]

Contents

Medical uses

Sitagliptin is used to treat type 2 diabetes.[2] It is generally less preferred than metformin or sulfonylureas.[3] It is taken by mouth.[2] It is also available as the fixed-dose combinations of sitagliptin/metformin (Janumet, Janumet XR)[2] and sitagliptin/simvastatin (Juvisync).[7]

Sitagliptin should not be used to treat type 1 diabetes. In December 2020, the U.S. Food and Drug Administration (FDA) approved labeling changes stating that Januvia (sitagliptin), Janumet (sitagliptin and metformin hydrochloride), and Janumet XR (sitagliptin and metformin hydrochloride extended-release) are not proven to improve glycemic (blood sugar) control in children aged 10 to 17 with type 2 diabetes.[8] The drugs are approved to improve blood sugar control in adults aged 18 and older with type 2 diabetes.[8]

Adverse effects

Adverse effects from sitagliptin are similar to placebo, except for rare nausea, common cold-like symptoms, and photosensitivity.[9] It does not increase the risk of diarrhea.[10] No significant difference exists in the occurrence of hypoglycemia between placebo and sitagliptin.[9][11][12] In those taking sulphonylureas, the risk of low blood sugar is increased.[13]

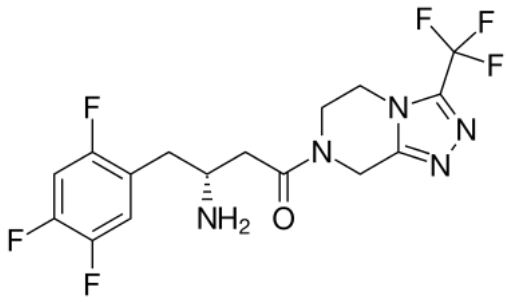
The existence of rare case reports of kidney failure and hypersensitivity reactions is noted in the United States prescribing information, but a causative role for sitagliptin has not been established.[14]

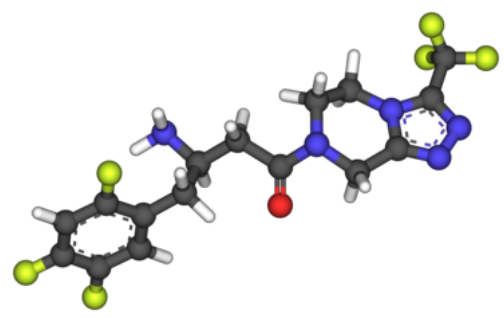
Several postmarketing reports of pancreatitis (some fatal) have been made in people treated with sitagliptin and other DPP-4 inhibitors,[15] and the U.S. package insert carries a warning to this effect,[16] although the causal link between sitagliptin and pancreatitis has not yet been fully substantiated.[17] One study with lab rats published in 2009 concluded that some of the possible risks of pancreatitis or pancreatic cancer may be reduced when it is used with metformin. However, while DPP-4 inhibitors showed an increase in such risk factors, as of 2009, no increase in pancreatic cancer has been reported in individuals taking DPP-4 inhibitors.[18]

The updated (August 2015) prescribing information cautions that multiple postmarketing reports have been made of serious hypersensitivity reactions in patients receiving sitagliptin. Merck notes:

> Additional adverse reactions have been identified during postapproval use of JANUVIA as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome; hepatic enzyme elevations; acute pancreatitis, including fatal and nonfatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute kidney injury (sometimes requiring dialysis); severe and disabling arthralgia; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; pemphigoid.[14]

Sitagliptin





Clinical data	
Pronunciation	/sɪtəˈglɪptɪn/ (listen)
Trade names	Januvia, Tesavel, Xelevia, others
AHFS/Drugs.com	Monograph (https://www.drugs.com/monograph/sitagliptin-phosphate.html)
MedlinePlus	a606023 (https://medlineplus.gov/druginfo/meds/a606023.html)
License data	EU EMA: by INN (http://www.ema.europa.eu/ema/index.jsp?curl=%2Fpages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keywordSearch=Submit&searchType=inn&taxonomyPath=&treeNumber=&searchGenericType=generics&keyword=Sitagliptin) US DailyMed: Sitagliptin (https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=Sitagliptin) US FDA: Sitagliptin (https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=Sitagliptin&SearchType=BasicSearch)
Pregnancy category	AU: B3
Routes of administration	By mouth
ATC code	A10BH01 (WHO (https://www.whocc.no/atc_

In 2015, the U.S. Food and Drug Administration (FDA) added a new Warning and Precaution about the risk of "severe and disabling" joint pain to the labels of all DPP-4 inhibitor medicines.[19] In addition to sitagliptin, other DPP-4 inhibitors such as saxagliptin, linagliptin, and alogliptin must also carry the new FDA Warning and Precaution label.

Mechanism of action

Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretins GLP-1 and GIP, gastrointestinal hormones released in response to a meal.[20] By preventing breakdown of GLP-1 and GIP, they are able to increase the secretion of insulin and suppress the release of glucagon by the alpha cells of the pancreas. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes, thus tending to prevent an "overshoot" and subsequent low blood sugar (hypoglycemia), which is seen with some other oral hypoglycemic agents.

Sitagliptin has been shown to lower HbA1c level by about 0.7% points versus placebo. It is slightly less effective than metformin when used as a monotherapy. It does not cause weight gain and has less hypoglycemia compared to sulfonylureas. Sitagliptin is recommended as a second-line drug (in combination with other drugs) after the combination of diet/exercise and metformin fails.[21]

History

Sitagliptin was approved by the U.S. Food and Drug Administration on October 17, 2006,[22] and is marketed in the US as Januvia by Merck & Co. On April 2, 2007, the FDA approved an oral combination of sitagliptin/metformin marketed in the US as Janumet. On October 7, 2011, the FDA approved an oral combination of sitagliptin/simvastatin marketed in the US as Juvisync.[7]

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	ddd_index/?code=A10BH01))
Legal status	
Legal status	AU: S4 (Prescription only) UK: POM (Prescription only) US: ℞-only EU: Rx-only
Pharmacokinetic data	
Bioavailability	87%
Protein binding	38%
Metabolism	Liver (CYP3A4- and CYP2C8-mediated)
Elimination half-life	8 to 14 h[1]
Excretion	Kidney (80%)[1]
Identifiers	
IUPAC name	(*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine
CAS Number	486460-32-6 (https://commonchemistry.cas.org/detail?cas_rn=486460-32-6) ✓
PubChem CID	4369359 (https://pubchem.ncbi.nlm.nih.gov/compound/4369359)
IUPHAR/BPS	6286 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=6286)
DrugBank	DB01261 (https://www.drugbank.ca/drugs/DB01261) ✓
ChemSpider	3571948 (http://www.chemspider.com/Chemical-Structure.3571948.html) ✓
UNII	QFP0P1DV7Z (https://fdasis.nlm.nih.gov/srs/unii/QFP0P1DV7Z)
KEGG	D08516 (https://www.kegg.jp/entry/D08516) as salt: D06645 (https://www.kegg.jp/entry/D06645)
ChEBI	CHEBI:40237 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:40237) ✓
ChEMBL	ChEMBL1422 (https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/ChEMBL1422) ✓
CompTox Dashboard (EPA)	DTXSID70197572 (https://comptox.epa.gov/dashboard/DTXSID70197572)
ECHA InfoCard	100.217.948 (https://echa.europa.eu/substance-information/-/substanceinfo/100.217.948)

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Chemical and physical data	
Formula	$C_{16}H_{15}F_6N_5O$
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3D model (JSmol)	Interactive image (https://chemapps.stolaf.edu/jmol/jmol.php?model=Fc1cc%28c%28F%29cc1F%29C%5BC%40%40H%5D%28N%29CC%28%3DO%29N3Cc2nnc%28n2CC3%29C%28F%29%28F%29F)
SMILES	Fc1cc(c(F)cc1F)C[C@@H](N)CC(=O)N3Cc2nnc(n2CC3)C(F)(F)F
InChI	InChI=1S/C16H15F6N5O/c17-10-6-12(19)11(18)4-8(10)3-9(23)5-14(28)26-1-2-27-13(7-26)24-25-15(27)16(20,21)22/h4,6,9H,1-3,5,7,23H2/t9-/m1/s1 ✓
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	(verify)

External links

- "Sitagliptin" (https://druginfo.nlm.nih.gov/drugportal/name/sitagliptin). *Drug Information Portal*. U.S. National Library of Medicine.