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(54) Title: MANUFACTURE, FORMULATION AND DOSING OF APRAGLUTIDE

AA Pos.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Native GLP-2	H	A	D	G	S	F	S	D	E	M	N	T	I	L	D	N	L	A	A	R	D	F	I	N	W	L	I	Q	T	K	I	T	D	OH					
Teduglutide	H	G	D	G	S	F	S	D	E	M	N	T	I	L	D	N	L	A	A	R	D	F	I	N	W	L	I	Q	T	K	I	T	D	OH					
Glepaglutide	H	G	E	G	T	F	S	S	E	L	A	T	I	L	D	A	L	A	A	R	D	F	I	A	W	L	I	A	T	K	I	T	D	K	K	K	K	NH ₂	
Apraglutide	H	G	D	G	S	F	S	D	E	Nle	D-Phe	T	I	L	D	L	L	A	A	R	D	F	I	N	W	L	I	Q	T	K	I	T	D	NH ₂					

Gly2 eliminates enzymatic cleavage by DPP-IV enzyme

Nle10, which does not contain sulfur, in place of Met10, eliminates formation of impurities which may form during chemical synthesis due to oxidation and alkylation of the sulfur atom of methionine.

Replacement of two asparagines, Asn11 by D-Phe11 and Asn16 by Leu16, causes a significant change in plasma protein binding and corresponding remarkable decrease in total clearance.

Change in C-terminus functionality from carboxylic acid to amide slows down the absorption from the SC injection site into the circulation increasing the terminal half-life. The lower charge due to the amide group is thought to result in a more limited solubility of the peptide and the formation of a transient "depot"

FIG. 1

(57) Abstract: The present disclosure relates to methods of making, formulating and administering GLP-2 analogs.

[Continued on next page]

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