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REVIEW

A Health Technology Assessment Based on Chinese Guidelines: Glucagon-Like Peptide-1 Receptor Agonist in the Treatment of Type 2 Diabetes Complicated with Cardiovascular Disease

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Purpose: According to the requirements of the "Quick Guide for Drug Evaluation and Selection in Chinese Medical Institutions", this health technology assessment provides an evidence-based basis for drug selection and rational clinical use of glucagon-like peptide-1 receptor agonist drugs in medical institutions.

Methods: We consult the drug instructions, clinical treatment guidelines and search relevant documents in databases such as China national knowledge infrastructure, Wanfang, PubMed, and government websites such as National Medical Products Administration, Food and Drug Administration, European Medicines Agency, and Pharmaceuticals and Medical Devices Agency to collect and sort out the relevant information of the indications, pharmacological effects, guideline recommendations, drug prices and other information of glucagon-like peptide-1 receptor agonists, using a percentile system systematically evaluate the five dimensions of glucagon-like peptide-1 receptor agonists in terms of pharmaceutical properties, efficacy, safety, economy, and other attributes.

Results: The final scores of the evaluation results from high to low are semaglutide (71.00 points), dulaglutide (68.75 points), liraglutide (67.50 points), exenatide (67.00 points), lixisenatide (63.50 points), polyethylene glycol loxenatide (58.00 points) and benaglutide (49.00 points).

Conclusion: In clinical practice, semaglutide and dulaglutide are the top two drugs that can be used as recommended drugs. This health technology assessment can provide an evidence-based basis for hospital selection and rational use of glucagon-like peptide-1 receptor agonists. Clinicians can rationally choose and use drugs according to the patient's conditions and needs.

Keywords: glucagon-like peptide-1 receptor agonist, hospital-based health technology assessment, drug selection and evaluation

Introduction

Hospital-based health technology assessment refers to applying the principles and methods of evidence-based medicine and health technology assessment, based on the actual needs of the hospital, to make a comprehensive and systematic evaluation of relevant health technologies and quick decisions for new technologies, access, use, etc. Improving the fairness of medical services is a commonly used policy analysis tool globally.[1,2]

Glucagon-like peptide-1 receptor agonist stimulates insulin and inhibits glucagon secretion by simulating natural glucagon-like peptide-1 to activate glucagon-like peptide-1 receptors, further inhibiting the appetite center to reduce food intake, and finally achieve the effect of lowering blood sugar. Cardiovascular disease in diabetic patients is the leading cause of death in diabetic patients. Diabetic patients are often associated with significant risk factors for cardiovascular disease, such as hypertension and dyslipidemia. The risk of cardiovascular disease in diabetic patients increases by 2–4 times. Glucagon-like peptide-1 receptor agonist has a significant hypoglycemic effect and has a small risk of hypoglycemia when used alone. At the same time, it has the functions of weight loss, blood pressure reduction, and improvement

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of blood lipid.[3] Selecting the appropriate glucagon-like peptide-1 receptor agonist can play a vital role in the condition of patients with type 2 diabetes mellitus and reduce the adverse reactions and economic burden caused by the use of other drugs. This study is based on the "Quick Guideline for Drug Evaluation and Selection in Chinese Medical Institutions" from clinical efficacy, pharmaceutical properties, safety, economy, and other attributes. The purpose is to carry out the health technology assessment for glucagon-like peptide-1 receptor agonist and provide evidence for hospital decision-makers to select drugs and use them rationally in clinical practice.

Methods

The research adopts a hundred-point evaluation model and is based on the "Quick Guide for Drug Evaluation and Selection of Chinese Medical Institutions"[4] released in 2020. We consult the drug instructions, clinical treatment guidelines and search relevant documents in databases such as China national knowledge infrastructure, Wanfang, PubMed, and government websites such as National Medical Products Administration, Food and Drug Administration, European Medicines Agency, and Pharmaceuticals and Medical Devices Agency to collect and sort out the relevant information of the indications, pharmacological effects, guideline recommendations, drug prices and other information of glucagon-like peptide-1 receptor agonists, using a percentile system systematically evaluate the five dimensions of glucagon-like peptide-1 receptor agonist in terms of pharmaceutical properties, efficacy, safety, economy, and other attributes (including national medical insurance, national essential medicine, global usage, manufacturer status), accounting for 20% each. Selection scope: The drugs selected and evaluated in this guideline are glucagon-like peptide-1 receptor agonist currently listed in China; they are exenatide injection, liraglutide injection, lixisenatide injection, benaglutide injection, dulaglutide injection, polyethylene glycol loxenatide injection, and semaglutide injection. This evaluation only includes the original drug/reference drug as the evaluation object. The basic information of GLP-1RAs is shown in Table 1.

Results

Pharmaceutical Properties Score

According to the drug registration data, drug instructions, authoritative guide, Chinese and English databases, information such as public announcements on the drug website of the State Drug Administration to investigate whether the medicines to be selected are superior to similar drugs or whether drugs can substitute them in five aspects: indications, pharmacological effects, in vivo processes, pharmacy and methods of use, and consistency evaluation.

Indications

Seven glucagon-like peptide-1 receptor agonists were used for glycemic control in adult patients with type 2 diabetes; among them, liraglutide, dulaglutide, and semaglutide had a risk reduction of major adverse cardiovascular events in adult patients with type 2 diabetes with cardiovascular disease, with a score of 3; exenatide, lixisenatide, benaglutide, and polyethylene glycol loxenatide all with a score of 1;

Table 1 Basic Information of GLP-1RAs

Common Name	Approved Regions (Time)
Exenatide Injection,	China (2009), Europe (2010), United States (2005), Japan (2010)
Liraglutide Injection	China (2011), Europe (2009), United States (2010), Japan (2010)
Lixisenatide Injection	China (2018), Europe (2013), United States (2016), Japan (2013)
Benaglutide Injection	China (2016)
Dulaglutide Injection	China (2019), Europe (2014), United States (2014), Japan (2015)
Polyethylene Glycol Loxenatide Injection	China (2019)
Semaglutide Injection	China (2021), Europe (2018), United States (2017), Japan (2018)

Pharmacy and Methods of Use

The ingredients and excipients of the seven glucagon-like peptide-1 receptor agonists are clear, the dosage form is appropriate, and the dosage is easy to master, with full scores. In terms of dosing frequency, exenatide twice daily, benaglutide three times daily, liraglutide and lixisenatide once daily, and dulaglutide, polyethylene glycol exenatide, and semaglutide once weekly; In terms of ease of use, all seven glucagon-like peptide-1 receptor agonists required training in medication operation, with a deduction of 0.5 points, Exenatide, lixisenatide, and benaglutide all had well-defined time periods with 0 points for each; liraglutide, dulaglutide, polyethylene glycol exenatide, and semaglutide could be administered at any time period with 0.5 points for each.

Pharmacological Effects, in vivo Processes and Consistency Evaluation

Seven glucagon-like peptide-1 receptor agonists had definite clinical efficacy, clear mechanism of action and in vivo process, complete pharmacokinetic parameters and were originators, with full scores; In summary, the pharmaceutical properties score results are shown in Table 2.

Efficacy Score

Drugs obtained evidence such as guideline recommendations by consulting guideline search tools such as Up to Date, Yaozhi Data, and Yimaitong. By consulting the database, domestic and foreign guidelines and consensus have recommended that glucagon-like peptide-1 receptor agonist can improve or treat patients with type 2 diabetes and cardiovascular disease to a certain extent, as shown in Table 3. Analysis of Table 3 shows that liraglutide, dulaglutide, and semaglutide injection are strongly recommended by multiple guidelines and expert consensus in the treatment of type 2 diabetes complicated with cardiovascular disease, and the level of evidence is I A; exenatide and lixisenatide injection are also mentioned in the guidelines and expert consensus as having a neutral effect on cardiovascular disease, and based on the results of the currently completed cardiovascular outcome study, cardiovascular effects of lixisenatide and exenatide were neutral, lixisenatide and exenatide injection have a neutral effect on the risk of heart failure hospitalization and can be considered for the treatment of heart failure patients with diabetes, the level of evidence is IIb A, but there are no other recommendations related to cardiovascular disease; There are no guidelines and expert consensus recommendations for benaglutide and polyethylene glycol loxenatide injection, and there is a lack of cardiovascular outcome research data.[5] The effectiveness score results are shown in Table 4.

Safety Score

According to drug instructions, drug registration data, safety information released by Food and Drug Administration, National Medical Products Administration and other government websites, English literature databases: PubMed, Embase, Chinese databases: China national knowledge infrastructure, and relevant domestic and foreign medication guidelines to evaluate the safety of seven glucagon-like peptide-1 receptor agonist drugs: adverse reactions grading, medication in special populations, adverse reactions due to drug interactions, reversibility of adverse reactions, teratogenicity and carcinogenicity, and special medication warnings.

Adverse Reaction Grading or CTCAE Grading

The most common adverse reactions to all seven glucagon-like peptide-1 receptor agonists were gastrointestinal reactions; Both benaglutide and polyethylene glycol loxenatide had mild-to-moderate renal impairment, hypoglycemia, gastrointestinal disorders, and injection site reactions without serious adverse effects, scoring 5; exenatide, liraglutide, and dulaglutide had rare necrotizing or hemorrhagic pancreatitis, acute kidney injury and renal failure (requiring hemodialysis), severe allergic reactions, severe hypoglycemia, scoring 4; lixisenatide and semaglutide had occasional severe hypoglycemia, severe allergic reactions, and acute pancreatitis, scoring 3;

Special Population

Seven glucagon-like peptide-1 receptor agonists are not recommended for use in children, pregnant women, and lactation, and none score, but liraglutide has been approved by the FDA for the treatment of type 2 diabetes in patients over 10 years of age, scoring 1. Seven glucagon-like peptide-1 receptor agonists can be used in the elderly population, with a score of 1. In terms of

Table 2 Pharmacological Properties Score Results

Pharmacological Properties (20 Points)		Grading Criteria	Exenatide	Liraglutide	Lixisenatide	Benaglutide	Dulaglutide	PEG Loxenatide	Semaglutide
Indications	Clinically necessary, preferred	3		3			3		3
	Clinical Need, Second Choice	2							
	More medicines available	1	1		1	1		1	
Pharmacological effects	Definite clinical efficacy and clear mechanism of action	3	3	3	3	3	3	3	3
	The clinical efficacy is definite, but the mechanism of action is not very clear	2							
	The clinical efficacy is general, and the mechanism of action is unclear	1							
In vivo processes	The in vivo process is clear and the pharmacokinetic parameters are complete	3	3	3	3	3	3	3	3
	The in vivo process is basically clear, and the pharmacokinetic parameters are incomplete	2							
	The in vivo process is not clear, no pharmacokinetic studies	1							
Pharmacy and methods of use (Multiple choice)	The main ingredients and excipients are clear	1	1	1	1	1	1	1	1
	Appropriate dosage form	2	2	2	2	2	2	2	2
	Dosing is easy to grasp	1	1	1	1	1	1	1	1
	Appropriate frequency of dosing	1	0	0.25	0.25	0	1	1	1
	Easy to use	1	0	0.5	0.25	0	0.5	0.5	0.5
Consistency evaluation	Original drug/reference drug	5	5	5	5	5	5	5	5
	Generic drugs that have passed the consistency evaluation	3							
	Non-original drugs or drugs that have not passed the consistency evaluation	1							
Pharmacological Properties Score			16.00	18.75	16.50	16.00	19.50	17.50	19.50

Table 3 Recommendations in Domestic and Foreign Guides and Consensus

Guide Name	Guideline Makers and Sources	Recommended Medications	Recommended Content	Evidence Level
2020 Guidelines for the prevention and treatment of type 2 diabetes in China[6]	Diabetes Branch of Chinese Medical Association	GLP-1RA with evidence of ASCVD benefit	GLP-1RA or SGLT2i with evidence of ASCVD benefit should be added to metformin in patients with type 2 diabetes with ASCVD or high cardiovascular risk, regardless of whether their HbA1c is up to standard or not, as long as there are no contraindications	A
Standards of Medical Care in Diabetes—2021[7]	American Diabetes Association	GLP-1RA with evidence of ASCVD benefit	SGLT2i or GLP-1 RAs with cardiovascular benefits are recommended as glucose-lowering therapy in T2DM patients with ASCVD or ASCVD high-risk factors, renal disease, or heart failure, regardless of baseline HbA1c levels.	A
Clinical Guidelines for Prevention and Treatment of Type 2 Diabetes in the Elderly in China (2022 Edition)[8]	Chinese Geriatrics Society Geriatric Endocrinology and Metabolism Branch, China Geriatric Health Medical Research Association	GLP-1RA with evidence of ASCVD benefit	In type 2 diabetes complicated with ASCVD or high-risk factors, CKD or HF, GLP-1RA is preferred according to individual patient conditions.	I A
Italian guidelines for the treatment of type 2 diabetes (2022)[9]	Italian Society of Diabetology, Italian Association of Medical Diabetologists	GLP-1RA	We recommend using metformin, SGLT-2 inhibitors or GLP-1 receptor agonists as first-line long-term treatment in patients with type 2 diabetes with previous cardiovascular events and without heart failure.	Strong Moderate
2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD[10]	European Society of Cardiology, European Association for the Study of Diabetes	Lixisenatide, Exenatide GLP-1RA with evidence of ASCVD benefit	1. Lixisenatide, liraglutide, semaglutide, exenatide and dulaglutide have a neutral effect on the risk of HF hospitalization and can be considered for the treatment of HF patients with diabetes 2. GLP-1RAs Liraglutide, semaglutide, or dulaglutide is recommended to reduce cardiovascular events in T2D patients with CVD or at very high/ high cardiovascular risk	II b A I A
CLINICAL PRACTICE GUIDELINES:MANAGEMENT OF TYPE 2 DIABETES MELLITUS (6th Edition)[11]	Ministry of Health Malaysia	Liraglutide, Dulaglutide, Semaglutide	In patients with type 2 diabetes with atherosclerotic cardiovascular disease, ASCVD or high risk, renal disease, or markers of heart failure, SGLT-2 inhibitors or GLP-1 RAs are recommended.	A

(*Continued*)

Table 3 (Continued).

Guide Name	Guideline Makers and Sources	Recommended Medications	Recommended Content	Evidence Level
2020 Guidelines on the management of diabetic patients. A position of Diabetes Poland[12]	Polskie Towarzystwo Diabetologiczne	GLP-1RA with evidence of ASCVD benefit	GLP-1RAs with established beneficial effects on cardiovascular risk should be considered first in patients with cardiovascular disease, especially before myocardial infarction	A
Clinical expert consensus on glucagon-like peptide-1 (GLP-1) receptor agonists for the treatment of type 2 diabetes[5]	Endocrinology Branch of Chinese Medical Association, Chinese Journal of Internal Medicine	Liraglutide, Dulaglutide, Semaglutide	1. It is recommended for type 2 diabetes patients with ASCVD or very high cardiovascular risk, which can reduce the risk of cardiovascular events.	/
2020 American College of Cardiology "Expert consensus decision pathway for novel therapies to reduce cardiovascular risk in patients with type 2 diabetes mellitus"[13]	American College of Cardiology	GLP-1RA with evidence of ASCVD benefit	Patients with T2DM with one or more ASCVD or high risk of ASCVD may choose GLP-1RA therapy with cardiovascular benefits.	/
Consensus Recommendations by the Asian Pacific Society of Cardiology: Optimizing Cardiovascular Outcomes in Patients with Type 2 Diabetes[14]	Asia-Pacific Society of Cardiology	GLP-1RA with evidence of ASCVD benefit	In patients with T2DM with normal renal function and high risk of cardiovascular events, GLP-1RA with proven cardiovascular benefit is recommended.	/
Expert consensus on the diagnosis and treatment of cardiovascular disease in patients with diabetes mellitus[15]	National Health Commission Capacity Building and Continuing Education Center	GLP-1RA with evidence of ASCVD benefit	In patients with ASCVD, the preferred GLP-1RA with proven cardiovascular benefit should be considered for glycemic and weight control.	/

Notes: GLP-1RA with cardiovascular benefits: liraglutide, dulaglutide, and semaglutide injection; these three drugs have been proved to have cardiovascular benefits by extensive clinical trials and have been approved by the United States FDA-approved for the treatment of patients with type 2 diabetes and cardiovascular disease.[16–21]
Abbreviations: CKD, chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease; SGLT2i, sodium-dependent glucose transporter 2 inhibitors.

Table 4 Efficacy Score Results

Efficacy (20 Points)	Grading Criteria	Exenatide	Liraglutide	Lixisenatide	Benaglutide	Dulaglutide	PEG Loxenatide	Semaglutide
Recommendations for diagnosis and treatment standards (National Health Administration)	20							
Guideline level I recommendation (level A evidence 18, level B evidence 17, level C evidence 16, other 15)	18		18			18		18
Guideline level II and below recommendations (level A evidence 14, level B evidence 13, level C evidence 12, other 11)	14	11		11				
Expert consensus recommendation	10							
None of the above are recommended	6				6		6	
Effectiveness Score		11	18	11	6	18	6	18

abnormal renal function, exenatide, benaglutide, and polyethylene glycol exenatide all had no relevant study data and scored 0, both lixisenatide and dulaglutide can be used with a score of 1, liraglutide and semaglutide can be used in mild-to-moderate renal dysfunction and are not recommended for severe, scoring 0.5 points. In terms of abnormal liver function, exenatide, lixisenatide, polyethylene glycol loxenatide, and semaglutide can be used in mild-to-moderate cases and are not recommended for severe cases, scoring 0.5 points, liraglutide and dulaglutide can be used in mild, moderate and severe forms and are not recommended for the terminal phase, scoring 0.75 points, benaglutide is not recommended, scoring 0.

Adverse Reactions Due to Drug Interactions

Seven glucagon-like peptide-1 receptor agonists will delay gastric emptying and affect the absorption rate of oral drugs. Patients taking oral medications that require rapid gastrointestinal absorption should be used with caution, scoring 1 point.

Reversibility of Adverse Reactions, No Teratogenic or Carcinogenic and No Special Medication Warning

Seven glucagon-like peptide-1 receptor agonists had special medication warnings, all of which scored 0. In terms of the reversibility of adverse reactions, they were basically reversible, with a score of 0.5 points. In terms of teratogenicity and carcinogenesis, exenatide was not teratogenic and carcinogenic, with a score of 1; liraglutide, dulaglutide, lixisenatide, and semaglutide were teratogenic and carcinogenic, with a score of 0; benaglutide was not teratogenic, but carcinogenicity study data were lacking, with a score of 0.5; polyethylene glycol loxenatide was not teratogenic, but carcinogenic, with a score of 0.5; In summary, the safety score results are shown in Table 5.

Table 5 Safety Score Results

Safety (20 Points)		**Grading Criteria**	**Exe**	**Lira**	**Lixise**	**Bena**	**Dula**	**PEG Loxe**	**Sema**
Adverse Reaction Grading or CTCAE Grading	Mild symptoms, no treatment required or CTC grade 1	7							
	Mild symptoms requiring intervention or CTC grade 2	6							
	Significant symptoms requiring intervention or CTC grade 3	5				5		5	
	Severe symptoms, life-threatening or CTC grades 4–5, incidence <0.1%	4	4	4			4		
	Severe symptoms, life-threatening or CTC grades 4–5, incidence 0.1–1%	3			3				3
	Severe symptoms, life-threatening or CTC grades 4–5, incidence 1–10%	2							
	Severe symptoms, life-threatening or CTC grades 4–5, incidence >10%	1							
Special population (multiple choices)	Can be used for children	2	0	1	0	0	0	0	0
	Can be used for the elderly	1	1	1	1	1	1	1	1
	Can be used for pregnant women	1	0	0	0	0	0	0	0
	Can be used by lactating women	1	0	0	0	0	0	0	0
	Can be used for abnormal liver function	1	0	0.5	1	0	1	0	0.5
	Can be used for abnormal renal function	1	0.5	0.75	0.5	0	0.75	0.5	0.5
Adverse reactions due to drug interactions	Mild to moderate: generally, no dose adjustment is required	3							
	Severe: Dose adjustment required	2							
	Taboo: Prohibited to use at the same time	1	1	1	1	1	1	1	1
Other (multiple choices)	Reversibility of adverse reactions	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	No teratogenic or carcinogenic	1	1	0	0	0.5	0	0.5	0
	No special medication warning	1	0	0	0	0	0	0	0
Safety Score			8.00	8.75	7.00	8.00	8.25	8.50	6.50

Economy Score

The seven GLP-1RAs are nationally negotiated drugs of China, and the price of the drugs is based on the latest national medical insurance negotiated drug prices (as of March 2022); the basic economy information is shown in Table 6: drug specifications, therapeutic dose and average daily treatment cost; the economy score results are shown in Table 7.

Other Attributes Score

National Medical Insurance and National Essential Medicine Attributes

Seven kinds of glucagon-like peptide-1 receptor agonists are medical insurance category B, semaglutide injection has no payment restrictions, and the other six injections have payment restrictions. Liraglutide injection is included in the

Table 6 Basic Economy Information

Economy	Exenatide	Liraglutide	Lixisenatide	Benaglutide	Dulaglutide	PEG Loxenatide	Semaglutide
Drug specification	1.2mL/piece (0.25mg/mL); 2.4mL/piece (0.25mg/mL);	3mL:18mg	0.05mg/mL, 3mL/piece;0.10mg/mL, 3mL/piece;	2.1mL:4.2mg (42000U)	0.5mL:1.5mg	0.5mL:0.1mg; 0.5mL:0.2mg	1.34mg/mL, 1.5mL/piece;1.34mg/mL, 3mL/piece;
Therapeutic dose	5μg 2 times daily for 1frist month; 10μg 2 times daily for 2nd to 7th month	0.6 mg daily for week 1; 1.2mg daily for week 2; 1.5mg daily for weeks 3–26	10μg daily for 1–2 weeks; 20μg daily for 3–24 weeks	0.1mg (50μL) 3 times/day for 1–2 weeks; 0.2mg (100μL) 3 times/day for weeks 3–12	0.75 mg weekly for 1–2 weeks; 1.5 mg weekly for 3–26 weeks	0.1mg weekly for 1–24 weeks	0.25mg weekly for 1–4weeks; 0.5mg weekly for 5–8weeks; 0.75mg weekly for 9–30weeks
Average daily treatment cost (¥)	12.80	27.38	17.26	25.03	20.47	15.71	18.90

Notes: Therapeutic dose according to the drug instructions, guidelines, expert consensus and consult the relevant literature where the recommended dose of hospital medication (starting dose + maintenance dose calculation); The medication cycle is the main treatment core week of the clinical trial according to the drug instructions; The maintenance dose of liraglutide injection of 1.5 mg/day is based on its clinical use of the average of 1.2 mg/day and 1.8 mg/day; The maintenance dose of semaglutide injection of 0.75 mg/day is based on its clinical use of the average of 0.5 mg/day and 1.0 mg/day.

Table 7 Economy Score Results

Economy (20 Points)		Grading Criteria	Exenatide	Liraglutide	Lixisenatide	Benaglutide	Dulaglutide	PEG Loxenatide	Semaglutide
Average daily treatment cost of the drug under evaluation	The lowest average daily treatment cost	20	20						
	Average daily treatment cost below median	17			17			17	
	Average daily treatment cost in the middle (median)	14							14
	Average daily treatment cost above median	11				11	11		
	The highest average daily treatment cost	8		8					
Economy Score			20	8	17	11	11	17	14

"National Essential Drugs List", and there is no Δ requirement, and the remaining six injections are not included in the "National Essential Drugs List".

Storage Conditions and Drug Expiration Date Attributes

The storage conditions of the seven glucagon-like peptide-1 receptor agonists required refrigeration. Exenatide, lixisenatide and semaglutide injections are valid for 36 months, and liraglutide injection is right for 30 months, polyethylene glycol loxenatide, benaglutide, and dulaglutide injections are right for 24 months.

Market and Companies' Attributes

Benaglutide and polyethylene glycol loxenatide injections have not been listed in the United States, Europe or Japan, and the remaining five injections have been listed in the United States, Europe and Japan. At the same time, the manufacturers of exenatide, liraglutide, lixisenatide, dulaglutide and semaglutide injection are among the world's top 50 pharmaceutical companies by sales, polyethylene glycol loxenatide injection are among the top 100 pharmaceutical industries of the Ministry of Industry and Information Technology, benaglutide injection is not among the top 100 pharmaceutical industries of the Ministry of Industry and Information Technology and the world's top 50 pharmaceutical companies by sales. The other attribute score results of the seven glucagon-like peptide-1 receptor agonists are shown in Table 8.

Table 8 Other Attribute Score Results

Other Attribute		Grading Criteria	Exe	Lira	Lixise	Bena	Dula	PEG Loxe	Sema
National medical insurance	National medical insurance category A, and no payment restrictions	5							
	National medical insurance category A, with payment restrictions	4							
	National Medical Insurance Category B/National Negotiated Drugs and No Payment Restrictions	3							3
	National medical insurance category B/national negotiated drugs, with payment restrictions	2	2	2	2	2	2	2	
	Not in the National Medical Insurance Directory	1							
National essential medicine	In the "National Essential Drug List", there is no Δ requirement	3		3					
	In the "National Essential Drug List", there are Δ requirements	2							
	Not in the "National Essential Medicines List"	1	1		1	1	1	1	1
Storage conditions	Normal temperature storage	3							
	Normal temperature storage, avoid or block light	2.5							
	Store in the shade	2							
	Store in the shade, avoid or block light	1.5							
	Refrigerated/frozen storage	1	1	1	1	1	1	1	1
Drug expiration date	>36 months	3							
	24~36 months	2	2	2	2	2	2	2	2
	< 24 months	1							
Global usage	Listed in the US, Europe and Japan	3	3	3	3		3		3
	Listed in the US or Europe or Japan	2							
	Not listed in the US, Europe and Japan	1				1		1	

(*Continued*)

Table 8 (Continued).

Other Attribute		Grading Criteria	Exe	Lira	Lixise	Bena	Dula	PEG Loxe	Sema
Production company status	The world's top 50 pharmaceutical companies by sales (US pharmaceutical managers)	3	3	3	3		3		3
	Manufacturers in the top 100 pharmaceutical industry list of the Ministry of Industry and Information Technology	2						2	
	Other enterprises	1				1			
Other attribute scores			12	14	12	8	12	9	13

Note: The "Δ" sign indicates that the drug should be used by a physician with corresponding prescription qualifications or under the guidance of a specialist physician, and use monitoring and evaluation should be strengthened.

Discussion

The final total score results for glucagon-like peptide-1 receptor agonist evaluations are shown in Table 9, semaglutide injection has the highest score among the seven target drugs, and the remaining glucagon-like peptide-1 receptor agonists are ranked in order of dulaglutide, liraglutide, exenatide, lixisenatide, polyethylene glycol loxenatide and benaglutide injection. According to the evaluation results, new drugs are introduced, among the seven glucagon-like peptide-1 receptor agonists, the top two semaglutide and dulaglutide can be used as recommended drugs. When adjusting medications, if there are many glucagon-like peptide-1 receptor agonist drugs (≥3 kinds) in medical institutions, high scoring drugs can be selected according to the score ranking. Drugs with lower scores are recommended to be temporarily reserved or transferred.

The evaluation results showed that all 7 GLP-1RAs had certain clinical value. Semaglutide, dulaglutide and liraglutide are currently the clinical first-choice drugs for type 2 diabetes complicated with cardiovascular disease, and evidence-based medicine is sufficient,[16–18] liraglutide 3.0mg and semaglutide 2.4mg have been approved by the FDA for weight management indications. The current cardiovascular outcomes of benaglutide and loxenatide are ongoing, and the results are promising. Both exenatide and lixisenatide have been confirmed to be neutral in cardiovascular research outcomes, that is, they will neither benefit nor adversely affect cardiovascular disease, and evidence-based medicine is sufficient.[20,21] In addition, the articles written by Qiu et al[22] have been initially applied to their area, and actions have also been initiated in other areas of the country. With further updates of the guidelines and other high-quality medical evidence, the results of this health technology assessment will be more comprehensive, reasonable, practical, and representative.

The hospital-based health technology assessment used in this study has the characteristics of being fast, convenient, scientific, objective, fair and comprehensive. Its evaluation results can solve the urgent decision-making problems for medical decision-makers and medical needs, such as drug selection and clinical rational use. It is the primary tool for

Table 9 Final Total Score Results for 7 GLP-1RA Drug Evaluations

Evaluation Dimension	Exenatide	Liraglutide	Lixisenatide	Benaglutide	Dulaglutide	Polyethylene Glycol Loxenatide	Semaglutide
Pharmaceutical properties	16.00	18.75	16.50	16.00	19.50	17.50	19.50
Efficacy	11	18	11	6	18	6	18
Safety	8.00	8.75	7.00	8.00	8.25	8.50	6.50
Economy	20	8	17	11	11	17	14
Other attributes	12	14	12	8	12	9	13
Total score	67.00	67.50	63.50	49.00	68.75	58.00	71.00

hospital decision makers to make drug decisions.[2] However, the domestic hospital-based health technology assessment started late, because the catalogue and pricing of medicines in most countries are formulated by the state, and the domestic also faces more challenges, such as difficult transformation decisions, professional composition of Hospital-based health technology assessment personnel single, lack of necessary interdisciplinary evaluation and other factors are easy to lead to the bias of evaluation results.

The purpose of this study is to provide evidence for the selection of the seven glucagon-like peptide-1 receptor agonists listed in China that best meet the needs of hospitals and clinical rational drug use, and these methods and practices of this health technology assessment can also serve as a reference for hospitals in other countries to select drugs. However, there are still many potential limitations in this review. For example, (1) This evaluation is only a quick and not a comprehensive evaluation, and its evaluation results are not widely representative. Each hospital needs to choose drugs according to the actual situation of its own hospital. (2) In clinical practice, clinicians will pay more attention to its effectiveness and safety. However, each dimension of this health technology assessment accounts for 20%. Without further research on the rationality of the proportions of each dimension, the results may be biased. (3) With the update of evidence-based medicine and pharmaceutical evidence, the extension of the clinical application time of drugs, the bidding and procurement of drugs, the adjustment of the national essential drug list, the adjustment of the National Medical Insurance Catalogue and the development of manufacturing enterprises, etc. The safety, effectiveness and economy of medicines will undergo certain changes; so that our evaluators need to update the evaluation rules in time to avoid biased evaluation results.

In order to make the evaluation results more comprehensive and representative, we need to fully follow the scientific concept of evidence-based medicine and emphasize the support of evidence for evaluation results, such as real-world multi-center clinical comprehensive evaluation and high-quality meta-analysis et al. At the same time, according to the hospital's goal of selecting drugs and rational drug use, through continuous practice and continuously optimize the coverage and weight of each index, enhance practicability and operability, and finally establish a convenient, comprehensive, effective, open and transparent evaluation tool suitable for medical institutions based on scientific methods, making the evaluation results more convincing and representative.

Conclusion

This health technology assessment can provide evidence-based evidence for the selection and rational use of glucagon-like peptide-1 receptor agonists in hospitals, and semaglutide and dulaglutide are the top two drugs that can be recommended. Hospitals can introduce GLP-1RA based on the results of this score or the needs of clinical practice, reducing the existing 7 types to 2 or 3 types, and clinicians can rationally choose and use drugs according to the patient's conditions and needs. At the same time, the methods and practices of this health technology assessment can also serve as a reference for hospitals in other countries to select drugs.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the jounal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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