

# Consensus on Rapid Clinical Evaluation of Angiotensin-Converting Enzyme Inhibitors

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## 1. Background

With the healthcare reform deepening and improving, China has been strengthening its focus on comprehensive evaluation of clinical drugs in recent years<sup>[1, 2]</sup>. This has led to the promotion of clinical comprehensive drug evaluation centered on people's health and guided by clinical value of drugs, which aims to promote the return of drugs to clinical value, consolidate and improve the basic drug system, and improve the drug supply chain system.

Cardiovascular disease is the leading cause of death and disease burden among Chinese residents<sup>[3]</sup>. From 1990 to 2019, the proportion of deaths caused by cardiovascular disease in total deaths increased from 25% to over 45% per year. The incidence of cardiovascular disease has also been increasing year by year. It is estimated that there are 330 million patients with cardiovascular disease nationwide, with diseases such as hypertension, coronary heart disease, and heart failure among the top five diseases<sup>[3]</sup>. The total cost of treating cardiovascular disease is also at the top of the list of disease-related expenses, resulting in heavy social and family burdens. Hypertension is a chronic disease with high morbidity, disability rate, and disease burden in China<sup>[3, 4]</sup>. Although the awareness, treatment, and control rates of hypertension in the Chinese population have improved in recent years, they are still at a relatively low level<sup>[5]</sup>. Hypertension is also the leading risk factor for cardiovascular disease burden<sup>[6]</sup>, with over 2 million premature deaths caused by high blood pressure each year in China, and direct medical costs amounting to ¥ 16.721 billion per year<sup>[3]</sup>. Angiotensin-converting enzyme inhibitors (ACEIs) are a class of drugs that exert antihypertensive effects by competitively inhibiting ACE. Since their introduction in the 1980s, a large amount of evidence-based medicine has shown that this class of drugs has good target organ protection and prevention of cardiovascular events in hypertensive patients<sup>[7-9]</sup>. ACEIs, with their significant antihypertensive effects and wide range of applications, have become one of the basic antihypertensive drugs, as well as a first-line therapy for heart failure<sup>[10, 11]</sup>. Although the mechanism of action of ACEIs is similar, there are still differences in pharmacological characteristics, adverse reactions, and economics. Therefore, it is

necessary to conduct comprehensive drug evaluation of ACEIs to provide reference for drug selection and optimization of drug list in medical institutions.

To date, there is no report on comprehensive clinical drug evaluation of ACEIs, and there is a lack of unified standards. Therefore, the Guangdong Pharmaceutical Association has organized pharmaceutical and clinical experts to develop this ACEI clinical rapid comprehensive evaluation expert consensus to help comprehensively evaluate the characteristics of this class of drugs. Since the research data on the brand name drugs of ACEIs available in China is comprehensive, this consensus uses them as representative evaluations. It serves as an illustrative evaluation methodology, offering a foundation for the subsequent clinical rapid comprehensive assessment of ACEI drugs across different medical institution

## **2. Methods and materials**

A Quick Guideline for Drug Evaluation and Selection in Chinese Medical Institution in 2020 ((hereinafter referred to as the "Quick Guide") has been published previously<sup>[12]</sup>, which uses a 100-point quantitative evaluation and establishes a quantitative scoring system for drug evaluation and selection (see in Table 1). Five dimensions, including pharmaceutical characteristics, effectiveness, safety, economy, and other attributes, are comprehensively evaluated for ACEI class drugs, aiming to provide scientific basis for hospital decision-makers to select and use drugs rationally in clinical practice. In addition, based on multiple expert discussions, this consensus adjusted the scoring of each evaluation dimension on the basis of the "Quick Guide," and refined some evaluation indicators to make the evaluation results more in line with clinical actual use. All adjustments were based on the opinions of 15 cardiovascular medical experts and 41 pharmaceutical experts in the Delphi questionnaire survey and voting, with the proportion of approval for the adjustment of scoring details ranging from 88.9% to 100%.

To ensure the authenticity, impartiality, and objectivity of drug information, the data collection of this consensus comes from the following materials and platforms: (1) Pharmaceutical characteristics and safety are obtained through searching drug instructions, drug registration materials, the website of the National Medical Products Administration, and Chinese and English databases (PubMed, Micromedex, UpToDate, CNKI, Wanfang, etc.). (2) Drug effectiveness is obtained through searching tools such as Medlive Online, Yaozhi data, and MCDEX. (3)

Drug prices are obtained through querying the "GuangDong Province Third-Party Drug Electronic Trading Platform." (4) Information on national medical insurance and essential drugs is obtained from the 2021 edition of the "National Medical Insurance, Work Injury Insurance, and Maternity Insurance Drug List" [13] and the 2018 edition of the "China National Essential Drug List" [14]. (5) Market information of drugs and information of production enterprises are obtained through searching drug information released by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, and the National Medical Products Administration (NMPA) of China. Some information of the production enterprises were obtained from the 2021 Pharm Exec Top 50 Companies<sup>[15]</sup>.

### **3. Indicators and definitions for rapid comprehensive clinical evaluation of pharmaceuticals**

#### **3.1 Pharmaceutical properties (24 points)**

The pharmaceutical properties of the drug under evaluation are examined in five aspects: indications (5 points), pharmacological effects (3 points), in vivo processes (3 points), pharmaceutical properties and usage methods (8 points), and consistency evaluation (5 points). Indication index assesses the clinical application status of the drug in treating diseases. However, in clinical practice, apart from reference to the instructions, clinical guidelines and authoritative guidelines are often used as research data, but these research materials often recommend a class of drugs together, making it difficult to distinguish their clinical application status. This consensus, based on expert opinions, adjusts the total score of the indication index to 5 points and adds additional points based on the coverage of indications, combining domestic and foreign instructions. In addition, the scoring rules for pharmaceutical properties and usage methods have been refined, and detailed rules can be found in Table 2.

#### **3.2 Efficacy (24 points)**

The clinical efficacy of the drug under evaluation is the focus of examination, assessing its recommended level in relevant authoritative professional materials, such as clinical guidelines, expert consensus, etc. Furthermore, in order to differentiate individual drugs in terms of efficacy, this consensus, based on the characteristics of ACEIs, adds additional scoring criteria. The clinical benefits of

ACEIs are derived from their blood pressure-lowering effects as well as their protective effects on target organs. Based on expert recommendations, this consensus uses blood pressure reduction, peak-to-trough ratio, and other clinical benefits as additional scoring criteria for efficacy. The maximum total score recommended by authoritative data has been adjusted to 12 points, and the total score for additional scoring criteria is 12 points (see Table 1 for details).

### **3.3 Safety (22 points)**

The safety of a drug is a crucial consideration during its evaluation, and it mainly examines its safety attributes in clinical applications in three first level indicators: adverse reaction classification using the Common Terminology Criteria for Adverse Events (CTCAE-V5.0) <sup>[16]</sup> (10 points), specific populations (9 points), and drug interactions caused adverse reaction (3 points). There are “other indicators” in the “Quick Guide” including the reversibility of adverse reactions, teratogenic and carcinogenic effects, and special medication warnings<sup>[12]</sup>. However, these three indicators cannot differentiate safety in drugs with similar safety attributes. The adverse reaction CTCAE system in the Quick Guide can only evaluate a single severe adverse reaction in the assessment of a specific drug. Thus, this consensus has eliminated the "other indicators" criteria and evaluated safety based on the severity of adverse reactions and their incidence rates. If the incidence rate is similar, it is also impossible to differentiate the safety in this aspect. Therefore, this consensus cancels the "Other" index and evaluates the adverse reactions of drugs according to the severity of adverse reactions and the incidence rate. In addition, this consensus has refined the scoring rules for specific populations <sup>[17]</sup>. The changes are as follows: Pediatric use (The use of drugs without special cautions will be assigned 2 points, use with cautions will be assigned 1 point, contraindications or not recommended to use will be assigned 0 points.); Geriatric use (The use of drugs without special cautions will be assigned 1 point, use with cautions will be assigned 0.5 points, contraindications or not recommended to use will be assigned 0 points.); Use during pregnancy and lactation (The use of drugs without special cautions will be assigned 1 point, use with cautions will be assigned 0.5 points, contraindications or not recommended to use will be assigned 0 points.). Because the degree of liver and kidney function impairment varies, drug selection is different. In order to facilitate clinical differentiation, this consensus has increased the weight of these two indicators and refined the scoring rules, specifically: patients with hepatic impairment and patients with renal impairment

(Drugs can be used without special cautions will be assigned 2 points; used with caution in patients with severe abnormalities will be assigned 1.0 point; used with caution with moderate to mild abnormalities will be assigned 0.5 points; contraindications or not recommended to use will get 0 points). (see in Table 1 for detail definition).

### 3.4 Economy (12 points)

This study only includes original/reference drugs as evaluation objects, using the "daily average treatment cost of the drug being evaluated (percentile)" as the of the economic aspect and set the score difference for each interval as 1 point.

### 3.5 Other features (18 points)

This indicator including six aspects: inclusion in the national medical insurance list, inclusion in the national essential drug list, storage conditions, drug expiration date, global usage (accessibility), and production company rating. As the national medical insurance directory is often updated and adjusted, the total score has been changed from 5 points (in Quick Guide) to 3 points, and the score difference for each interval is set to 0.5 points in our consensus.

The Quantitative record form for drug evaluation and selection in medical institutions is shown in Table 1

**Table 1 Quantitative record form for drug evaluation and selection in medical institutions**

<b>Indicators (Up to points)</b>	<b>Definition</b>
<b>1. Pharmaceutical properties (24)</b>	
<b>Indications (5)</b>	Essential and first line drugs score 3 points. Necessary but second-line drugs score 2 points. Many alternatives available score 1 points. Bonus if match other criteria score up to 2 points.
<b>Pharmacology (3)</b>	Efficacy is well-established, and the mechanism of action is clearly defined score 3 points. Efficacy and mechanism of action is not well-established score 2 points. Efficacy and mechanism of action is not clear score 1 point.
<b>Metabolism (3)</b>	Clear understanding of in vivo processes and complete pharmacokinetic parameters score 3 points.

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	The basic understanding of the in vivo processes is established, but the pharmacokinetic parameters are incomplete score 2 points
	In vivo process is not yet clear, and there is no pharmacokinetic research available score 1 point.
<b>Pharmaceutics and methods of administration</b>	The main ingredients and excipients are clearly identified score 1 point.
	Dosage form is suitable score 2 points.
<b>(8). Details are shown in Table 2.</b>	The dosing regimen is easily manageable and comprehensible score 1 point.
	Dosing frequency is appropriate score 3 points.
	Easy to use score 1 point.
<b>Already undergone Therapeutic Evaluations (5)</b>	Brand name drugs/ Reference Listed Drug score 5 points.
	Generic drugs undergone therapeutic equivalence evaluation score 3 points.
	None of the above score 1 point.
<b>2. Efficacy (24)</b>	
<b>Recommendations from authoritative medical literature (12)</b>	Recommendations from national clinical practice guidelines or national clinical pathway score 12 points.
	Recommendations from clinical practice guidelines, Class I (Up to 11 points: 11 points for level A, 10 points for level B, 9 points for level C, 8 points for evidence level lower than C).
	Recommendations from clinical practice guidelines, Class II or lower (Up to 7 points: 7 points for level A, 6 points for level B, 5 points for level C, 4 points for evidence level lower than C).
	Recommendations from expert consensus score 3 points.
	None of the above score 2 points.
<b>The magnitude of blood pressure reduction (2)</b>	The magnitude of blood pressure reduction. (Up to 2 points.)
<b>Trough/Peak ratio (2)</b>	Two points if Trough/Peak ratio $\geq 50\%$ and one point if Trough/Peak ratio below 50%.
<b>Other clinical benefit (8)</b>	Evidence of clinical benefits of the drug in target populations with specific indications (cardiovascular, renal).
<b>3. Safety (24)</b>	
<b>Adverse reaction classification using the</b>	The incidence of mild to moderate adverse reactions. (point 5 if rate $< 0.01\%$ or very rare; point 4 if rate is between 0.01% and 0.1% or rare;

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<b>Common Terminology Criteria for Adverse Events (CTCAE-V5.0) (10)</b>	<p>point 3 if rate is between 0.1% and 1% or uncommon; point 2 if rate is between 1% and 10% or common; point 1 if rate <math>\geq 10\%</math> or very common).</p> <p>If the incidence rate is within the same range, deduct 1 point from drugs that have a higher incidence rate compared to similar medications.</p> <p>The incidence of severe adverse reactions. (point 5 if rate <math>&lt; 0.01\%</math> or very rare; point 4 if rate is between 0.01% and 0.1% or rare; point 3 if rate is between 0.1% and 1% or uncommon; point 2 if rate is between 1% and 10% or common; point 1 if rate <math>\geq 10\%</math> or very common).</p>
<b>Specific populations (9)</b>	<p>Pediatric use (Up to 2 points: use without special cautions will get 2 points, use with cautions will get 1 point, contraindications or not recommended to use will get 0 points.)</p> <p>Geriatric use (Up to 1 point: Drugs can be used without special cautions will be assigned 1 point, use with cautions will be assigned 0.5 points, contraindications or not recommended to use will be assigned 0 points.)</p> <p>Pregnancy (Up to 1 point: Drugs can be used without special cautions will be assigned 1 point, use with cautions will be assigned 0.5 points, contraindications or not recommended to use will be assigned 0 points.)</p> <p>Lactation (Up to 1 point: Drugs can be used without special cautions will be assigned 1 point, use with cautions will be assigned 0.5 points, contraindications or not recommended to use will be assigned 0 points.)</p> <p>Hepatic impairment (Up to 2 points: Drugs can be used without special cautions will be assigned 2 points; used with caution in patients with severe abnormalities will be assigned 1.0 point; used with caution with moderate to mild abnormalities will be assigned 0.5 points; contraindications or not recommended to use will get 0 points)</p> <p>Renal impairment (Up to 2 points: Drugs can be used without special cautions will be assigned 2 points; used with caution in patients with severe abnormalities will be assigned 1.0 point; used with caution with moderate to mild abnormalities will be assigned 0.5 points; contraindications or not recommended to use will get 0 points)</p>
<b>Exists adverse interacting caused by drug interaction. (3)</b>	<p>Mild to moderate: Generally, no dose adjustment of medication is required. Score 3 points.</p> <p>Severe: need to adjust dosage. Score 2 points.</p> <p>Contraindications: should not be used concomitantly. Score 1 point.</p>

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#### 4. Economy (12)

**Average daily therapeutic cost of evaluated drugs (percentile)**     $\leq 20\%$  percentile score 12 points.  
20%~40% percentile score 11 points.  
40%~60% percentile score 10 point.  
60%~80% percentile score 9 point.  
80%~100% percentile score 8 point.

#### 5. Other features (18)

**Inclusion in the national reimbursement drug list (NRDL) (3)**    Drug was selected into Categories A of the China National Reimbursement Drug List (NRDL), and without payment restrictions score 3 points.

Drug was selected into Categories A of the China NRDL, but with payment restrictions score 2.5 points.

Drug was selected into Categories B of the China NRDL, and without payment restrictions score 2 points.

Drug was selected into Categories B of the China NRDL, but with payment restrictions score 1.5 points.

Not selected into the China NRDL score 1 point.

**Inclusion in the national essential drug list (3)**    Drug is in the national essential drug list, without symbol “ $\triangle$ ” score 3 points.

Drug is in the national essential drug list, with a symbol “ $\triangle$ ” score 2 points.

Drug is not a national essential drug score 1 points.

**Storage conditions (3)**    Can be stored in room temperature score 3 points.

Can be stored in room temperature and away from light or in a light-resistant container score 2.5 points.

Should be stored in cool place score 2 points.

Should be stored in cool place score and away from light or in a light-resistant container 1.5 points.

Should be stored in a refrigerated or frozen condition score 1 point.

**Expiration date (3)**    Expiration date  $>36$  months score 3 points.

Expiration date ranking 24~36 months score 2 points.

Expiration date  $<24$  months score 1 point.

**Global market approval status (3)**    Already marketed in the United States, Europe, and Japan score 3 points.

Already marketed in the United States, Europe, or Japan score 2 points.

Not marketed in the United States, Europe, and Japan score 1 point.

**Manufacturing company**    Top 50 pharmaceutical companies (according to Pharmaceutical Executive,

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<b>rating (3)</b>	United States) score 3 points. Top 100 enterprises of Ministry of Industry and Information Technology of the People's Republic of China score 2 points. Other companies score 1 point.
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The symbol "△" indicates that the drug should be used under the guidance of a qualified physician or a specialist physician, and the drug monitoring and evaluation should be strengthened.

**Table 2 Detail scoring rules in terms of pharmaceuticals and methods of administration**

Indicators and Definitions		Score
The main ingredients and excipients. (1)	Both the main ingredients (biomacromolecules, peptide chains with unclear relative molecular weight, or unclear structure) and excipients are clear.	1.0
	The main ingredients or excipients are not clear.	0.8
	Neither the main ingredients nor excipients are clear.	0.5
Dosage form is suitable (2)	Oral formulations, topical preparations.	2.0
	Subcutaneous injection, intramuscular injection, and muscle injection preparations.	1.5
	Intravenous injection, intravenous drip.	1.0
The dosing regimen is easily manageable and comprehensible. (1)	No dosage adjustment is needed during the treatment process, and no calculation of dosage based on body weight, body surface area, etc. is required	1.0
	Dosage adjustment needed during the treatment course, such as doubling the initial dose, adjusting the dose according to laboratory values, etc.	0.8
	Routine dose adjustment is necessary, and the dosage should be calculated based on body weight or body surface area.	0.5
Dosing frequency is appropriate (3).	Once daily.	3
	Twice daily.	2
	Thrice daily.	1
Easy to use (1)	Self-administration without the need for medical personnel or assistance from others.	1.0
	Can be self-administered with the assistance of others or with clear instructions on medication use, without the need for medical personnel.	0.8
	Need to be administered under the assistance of healthcare professionals.	0.5

#### 4. Evaluations for ACEIs

Scope: The ACE inhibitors evaluated in this consensus are those that have been

marketed in China, including captopril, benazepril, enalapril, perindopril, ramipril, fosinopril, and imidapril. Only the brand name drugs/reference preparations were included in this evaluation. It should be noted that lisinopril is a national essential medicine and has an important position <sup>[14]</sup>, however, the original product is no longer marketed in China, relevant evaluation information cannot be obtained, therefore, it was not evaluated in this consensus. There are two varieties of perindopril, perindopril tert-butylamine and perindopril arginine, but since perindopril arginine is only available in compound preparations currently marketed in China, the perindopril evaluated in this consensus refers to perindopril tert-butylamine. For specific information on the evaluated drug varieties, please refer to Table 3.

**Table 3 Brand name drugs of ACEIs in China**

<b>Generic Name in Chinese</b>	<b>Generic Name</b>	<b>Brand name in Chinese</b>	<b>Brand name</b>	<b>Manufacturing enterprise</b>
卡托普利	Captopril	开博通	Capoten <sup>®</sup>	Bristol Myers Squibb
贝那普利	Benazepril	洛汀新	Lotensin <sup>®</sup>	Novartis
依那普利	Enalapril	悦宁定	Renitec <sup>®</sup>	Merck Sharp & Dohme
培哌普利	Perindopril	雅施达	Acertil <sup>®</sup>	SERVIER
雷米普利	Ramipril	瑞泰	Tritace <sup>®</sup>	Sanofi
福辛普利	Fosinopril	蒙诺	Monopril <sup>®</sup>	Bristol Myers Squibb
咪达普利	Imidapril	达爽	Tanatril <sup>®</sup>	Mitsubishi Tanabe Pharma

## **4.1 Pharmaceutical characteristics**

### **4.1.1 Indications**

In the evaluation of indications, the domestic and foreign drug package inserts of the seven ACE inhibitors were comprehensively evaluated and scored. All the evaluated ACE inhibitors have hypertension indications in their domestic package inserts, which belong to drugs with many alternatives and are scored 1 point. ACE

inhibitors play an important role in the treatment of heart failure, so those with heart failure indications are scored 2 points. In addition, according to domestic and foreign package inserts, other indications are scored as additional points, up to 2 points. According to the approved indications in domestic package inserts, all the ACE inhibitors evaluated in this consensus have hypertension indications, and except for imidapril, they all have heart failure indications. In addition, ramipril can also be used to reduce the risk of myocardial infarction, stroke, and cardiovascular death in non-diabetic kidney disease patients and in patients with coronary heart disease.

In the FDA-approved indications in the United States, captopril's indications also include left ventricular dysfunction after myocardial infarction and diabetic nephropathy in type 1 diabetes patients; perindopril is also used in stable coronary heart disease patients to reduce cardiovascular death or non-fatal myocardial infarction risk. The Japanese package insert indicates that imidapril has indications for diabetic nephropathy in type 1 diabetes patients. The indications in the EMA's package insert are similar to those in the FDA-approved indications.

Based on the above analysis, the scores for the evaluated ACEI drugs are as follows: 5 points for captopril and ramipril, 4 points for perindopril, 2 points for moexipril, and 3 points for the other ACEI drugs.

#### **4.1.2 Pharmacology**

The seven types of ACE inhibitors evaluated in this consensus have demonstrated clinical efficacy and clear mechanisms of action, warranting a score of 3 for pharmacological effects.

#### **4.1.3 Metabolism**

The pharmacokinetic parameters of absorption, distribution, metabolism, and excretion of the 7 ACEI drugs evaluated are well-defined, and therefore, all received a score of 3.

#### **4.1.4 Pharmaceutical properties and in terms of usage**

This consensus has established more detailed scoring rules for this evaluation indicators<sup>[17]</sup>, as shown in Table 3. Although the package inserts in China of the 7 ACEI drugs evaluated in this consensus do not display excipients, they are clearly indicated in foreign package inserts. Therefore, we believe that both the main ingredients and excipients are clear, and thus receive 1 point each. All 7 drugs are oral preparations, which receive 2 points. In terms of appropriate dosing frequency, due to its short half-life, captopril usually requires 3 times daily administration,

hence receives 1 point. Benazepril and enalapril sometimes require twice daily administration, hence receive 2 points. The other ACEI drugs can be taken once daily, and thus receive 3 points.

#### 4.1.5 Undergone therapeutic equivalence evaluations

All 7 ACEI drugs evaluated in this consensus are branded/original drugs or reference products, and therefore scored 5 points. Detailed scoring information are shown in Table 4.

**Table 4 Pharmaceutical properties**

<b>Pharmaceutical Properties</b> (Up to 24 point)	Scoring criteria (Up to points)	Capto pril	Benaz epril	Enala pril	Perind opril	Ramip ril	Fosin opril	Imida pril
Indications (5)	Essential and first line drugs score (3)	3	3	3	3	3	3	1
	Necessary but second-line (2)							
	Many alternatives available (1)							
	Bonus (2)	2			1	2		1
Pharmacology (3)	Efficacy is well-established, and the mechanism of action is clearly (3)	3	3	3	3	3	3	3
	Efficacy or mechanism of action is not well-established (2)							
	Efficacy and mechanism of action is not clear (1)							
Metabolism (3)	Clear understanding of in vivo processes and complete pharmacokinetic parameters (3)	3	3	3	3	3	3	3
	The basic understanding of the in vivo processes is established, but the pharmacokinetic parameters are incomplete (2)							
	In vivo process is not yet clear, and there is no							

	pharmacokinetic research available (1)							
Pharmaceutics and methods of administration (8).	Main ingredients and excipients are clearly identified (1)	1	1	1	1	1	1	1
	Dosage form is suitable (2)	2	2	2	2	2	2	2
	The dosing regimen is easily manageable and comprehensible (1)	0.8	0.8	0.8	0.8	0.8	0.8	0.8
	Dosing frequency is appropriate (3)	1	2	2	3	3	3	3
	Easy to use score (1)	1	1	1	1	1	1	1
<b>Undergone Therapeutic Equivalence Evaluations</b>	Brand name drugs/ Reference Listed Drug (5)	5	5	5	5	5	5	5
	Generic drugs undergone therapeutic equivalence evaluation (3)							
	None of the above score (1)							
<b>Total score</b>		<b>21.8</b>	<b>20.8</b>	<b>20.8</b>	<b>22.8</b>	<b>23.8</b>	<b>21.8</b>	<b>20.8</b>

## 4.2 Efficacy score for ACEIs

### 4.2.1 Recommendations from authoritative medical literature on hypertension

The national guideline in 2018 [18] or regulatory compliance in 2019 [19] for hypertension published by the China National Cardiovascular Center recommend all ACE inhibitors included in this consensus. Additionally, 2018 ESC/ESH Guidelines for the management of arterial hypertension [20] also list ACE inhibitors as first-line antihypertensive drugs. Therefore, they are all awarded 12 points in this indicator.

### 4.2.2 The magnitude of blood pressure lowering and the trough-to-peak ratio.

Lowering blood pressure is one of the reasons why ACE inhibitors provide clinical benefits, and the trough-to-peak ratio of antihypertensive drugs is also an important indicator for evaluating efficacy [21]. This consensus evaluated various ACE inhibitors based on the magnitude of blood pressure lowering and the trough-to-peak ratio, using data from relevant studies and meta-analyses [22, 23]. A Cochrane systematic review [24] analyzed the blood pressure-lowering effects of ACE

inhibitors in primary hypertension, and this consensus used the data from that study to rate the drugs based on the recommended maximum doses in the package inserts for the reduction in systolic and diastolic blood pressure.

### **4.2.3 Others benefits**

ACE inhibitors have organ-protective effects independent of their blood pressure-lowering effects. This consensus references authoritative guidelines in the fields of heart failure, coronary heart disease (stable angina, acute myocardial infarction), and kidney disease to evaluate the clinical benefits of ACE inhibitors using evidence-based scoring. The heart failure and coronary heart disease guidelines are based on grade A evidence<sup>[10, 11, 25, 26]</sup>, and therefore carry a maximum weighting of 3 points each, while the kidney disease guideline is based on grade B evidence<sup>[27, 28]</sup>, carrying a maximum weighting of 2 points. If authoritative guidelines or clinical practice recommendations for each disease specify particular drugs, points are assigned based on the number of guidelines recommending those drugs; otherwise, points are assigned based on the evidence supporting the recommendations.

The 2018 Chinese Heart Failure Guidelines<sup>[29]</sup> has list commonly used ACEIs, all of which except perindopril are recommended as common drugs. The 2022 version of the Heart Failure Management Guidelines<sup>[10]</sup> from the American Heart Association (AHA) and other organizations also recommend drugs, and all ACE inhibitors evaluated in this consensus, except benazepril and perindopril, are common ACE inhibitors recommended in that guideline. The 2021 European Society of Cardiology (ESC) Heart Failure Guidelines<sup>[11]</sup> recommend the use of the ACE inhibitors evaluated in this consensus, namely captopril, enalapril, and ramipril.

Clinical pathways or guidelines related to myocardial infarction<sup>[30]</sup> and coronary heart disease<sup>[31, 32]</sup> in China recommend ACE inhibitors. Stable Coronary Heart Disease Diagnosis and Treatment Guidelines<sup>[32]</sup> recommend ACE inhibitors to improve long-term prognosis based on evidence for perindopril<sup>[33]</sup> and ramipril<sup>[34]</sup>. Both the 2017 ESC Guidelines for the Management of ST-Elevation Myocardial Infarction<sup>[35]</sup> the 2020 ESC Clinical Practice Guidelines on Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation<sup>[25]</sup> recommend ACE inhibitors to reduce all-cause mortality, cardiovascular mortality, and cardiovascular events (primarily based on evidence for captopril<sup>[36, 37]</sup>, enalapril<sup>[38]</sup>, perindopril<sup>[39, 40]</sup>, and ramipril<sup>[41]</sup>).

All ACEIs are recommended in the 2021 Edition of the Chinese Guidelines for the

Prevention and Treatment of Diabetic Kidney Disease<sup>[42]</sup>. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Management of Diabetes in Chronic Kidney Disease Patients 2022<sup>[27]</sup> and 2021 KDIGO Clinical Practice Guidelines for Glomerulonephritis <sup>[43]</sup> recommend ACE inhibitors for the treatment of proteinuria in diabetic and non-diabetic patients to reduce cardiovascular events, delay the progression of kidney disease, and prevent end-stage kidney disease. Except for perindopril, all other ACE inhibitors in this consensus are recommended drugs in the guidelines.

Based on the above results, this consensus provides scoring results for other clinical benefits of ACE inhibitors. The scores are as follows: captopril 6.5 points, benazepril 3 points, enalapril 5.5 points, perindopril 7 points, ramipril 8 points, fosinopril 4 points, and imidapril 0 points.

Table 5 provides a detailed breakdown of the efficacy ratings for ACEIs.

**Table 5 Efficacy evaluation for ACEIs**

	Scoring criteria (Up to points)	Capt opril	Bena zepril	Enala pril	Perin dopri l	Rami pril	Fosin opril	Imid april
<b>Recommendations from authoritative medical literature (Up to 12 points)</b>	Recommendations from national clinical practice guidelines or national clinical pathway. (12)	12	12	12	12	12	12	12
	Recommendations from clinical practice guidelines, Class I (Up to 11)							
	Recommendations from clinical practice guidelines, Class II or lower. (Up to 7)							
	Recommendations from expert consensus (3).							
	None of the above score 2 points.							
	Blood pressure reduction (2)	2	1.5	1.5	1.5	1	1.5	1.5
<b>Trough/Peak ratio</b> ( $\geq 50\%$ score 2 points, otherwise score 1 point)	1	1	2	1	2	2	2	
Other clinical benefit (8)	6.5	3	5.5	7	8	4	0	
<b>Total (24)</b>		<b>21.5</b>	<b>17.5</b>	<b>21</b>	<b>21.5</b>	<b>23</b>	<b>19.5</b>	<b>15.5</b>

### 4.3 Safety

### **4.3.1 Adverse reaction classification using the Common Terminology Criteria for Adverse Events (CTCAE-V5.0)**

The present consensus employs the CTCAE grading system to classify adverse events into mild-to-moderate and severe categories, giving greater weight to those with lower incidence rates. Mild-to-moderate adverse events primarily include dry cough, rash, and mild-to-moderate granulocytopenia. The incidence rates of mild-to-moderate adverse events are commonly observed across all ACEI drug classes, with relatively higher rates observed for captopril, enalapril, and ramipril <sup>[44]</sup>, warranting a score of 1, while the remaining four ACEI drug classes receive a score of 2. Severe adverse events are primarily assessed based on the incidence of angioneurotic edema and are rare for all ACEI drug classes, warranting a score of 3 points.

### **4.3.2 Specific population**

Clinical data for enalapril in children over 1 year of age is available, while captopril is only limited to pediatric patients for whom other antihypertensive therapies are ineffective. Therefore, enalapril and captopril receive 2 points. Benazepril can be used in children over 6 years of age, and fosinopril can be used in children over 12 years of age. Although the package insert for ramipril does not recommend its use in children, the European Society of Hypertension Guidelines for the Management of Hypertension in Children and Adolescents<sup>[45]</sup> provide dosage recommendations for this medication. Therefore, these four drugs are given 1 point each. Perindopril and moexipril are not recommended for use in children according to their package inserts, and there are no relevant guidelines recommending their use, thus they receive 0 points. All ACE inhibitors are contraindicated in pregnant women; therefore, they all receive 0 points. Regarding lactation, fosinopril is contraindicated in lactating women, and perindopril and ramipril are not recommended for use in lactating women. Therefore, these three drugs receive 0 points. Although the package insert for benazepril does not recommend its use in lactating women, there are guidelines recommending its use <sup>[46]</sup>, and the package inserts for captopril and enalapril suggest caution in use in lactating women. Therefore, these three ACE inhibitors receive 0.5 points. For the criterion of use in patients with liver dysfunction, fosinopril and perindopril do not require dosage adjustment in patients with impaired liver function, and benazepril is not affected by hepatic damage, thus they receive 2 points. Other ACE inhibitors are cautioned in severe liver dysfunction, so they receive 1 point. Regarding the criterion of use



in patients with renal dysfunction, fosinopril does not require dosage adjustment in patients with decreased renal function, thus it receives 2 points. Captopril is cautioned in patients with mild renal dysfunction; thus, it receives 0.5 points. For other ACE inhibitors, caution is advised in severe renal dysfunction (eGFR < 30 ml/min), and dosage adjustment is necessary, therefore they receive 1 point.

#### 4.3.3 Exists adverse interacting caused by drug interaction.

All ACE inhibitors are contraindicated for concomitant use with drugs containing aliskiren and should be avoided in combination with sacubitril/valsartan. Therefore, this criterion is given a score of 1. For specific scoring details, please refer to Table 6.

**Table 6 Safety evaluation for ACEIs**

Safety (Up to 20 points)	Scoring criteria (Up to points)	Captopril	Benazepril	Enalapril	Perindopril	Ramipril	Fosinopril	Imidapril
Adverse reaction classification (10)	The incidence of mild to moderate adverse reactions. (point 5 if rate <0.01% or very rare; point 4 if rate is between 0.01% and 0.1% or rare; point 3 if rate is between 0.1% and 1% or uncommon; point 2 if rate is between 1% and 10% or common; point 1 if rate ≥10% or very common). If the incidence rate is within the same range, deduct 1 point from drugs that have a higher incidence rate compared to similar medications.	1	2	1	2	1	2	2
	The incidence of severe adverse reactions. (point 5 if rate <0.01% or very rare; point 4 if rate is between 0.01% and 0.1% or rare; point 3 if rate is between 0.1% and 1% or uncommon; point 2 if rate is between 1% and 10% or common; point 1 if rate ≥10% or very common).	3	3	3	3	3	3	3

Specific populations (9)	Pediatric use (2)	2	1	2	0	1	1	0
	Geriatric use (1)	1	1	1	1	1	1	0.5
	Pregnancy (1)	0	0	0	0	0	0	0
	Lactation (1)	0.5	0.5	0.5	0	0	0	0.5
	Hepatic impairment (2)	1	2	1	2	1	2	1
	Renal impairment (2)	0.5	1	1	1	1	2	1
Exists adverse interacting caused by drug interaction. (3)	Mild to moderate: Generally, no dose adjustment of medication is required. (3)							
	Severe: need to adjust dosage. Score 2 points. (2)							
	Contraindications: should not be used concomitantly. Score 1 point. (1)	1	1	1	1	1	1	1
Total		<b>10</b>	<b>11.5</b>	<b>10.5</b>	<b>10</b>	<b>9</b>	<b>12</b>	<b>9</b>

#### 4.4 Economy

The daily cost of each drug was evaluated based on the World Health Organization's Defined Daily Dose (DDD) reference, calculated using the minimum unit price. The DDD values for each drug were as follows: 50mg/day for captopril, 7.5mg/day for benazepril, 10mg/day for enalapril, 4mg/day for perindopril, 2.5mg/day for ramipril, 15mg/day for fosinopril, and 10mg/day for moexipril. The drug prices were based on the same generic name and sourced from the "GuangDong Third-Party Drug Electronic Trading Platform", rounded to two decimal places. The daily costs were ¥3.60 for captopril, ¥3.36 for benazepril, ¥1.27 yuan for enalapril, 2.69 yuan for perindopril, 2.43 yuan for ramipril, 1.26 yuan for fosinopril, and 2.83 yuan for moexipril. The specific scoring details for the economic evaluation are shown in Table 7.

**Table 7 Economy evaluation for ACEIs**

<b>Economy (Up to 12 points)</b>	<b>Total (24)</b>	<b>Capt opril</b>	<b>Ben azep ril</b>	<b>Enal april</b>	<b>Peri ndop ril</b>	<b>Ram ipril</b>	<b>Fosi nopr il</b>	<b>Imid april</b>

Average daily therapeutic cost of evaluated drugs (percentile)	≤20% percentile score (12)							
	20%~40% percentile score 11 points.			11			11	
	40%~60% percentile score 10 point.							
	60%~80% percentile score 9 point.				9	9		9
	60%~80% percentile score 9 point. (8)	8	8					
<b>Total (12)</b>		<b>8</b>	<b>8</b>	<b>11</b>	<b>9</b>	<b>9</b>	<b>11</b>	<b>9</b>

## 4.5 Other features

### 4.5.1 Inclusion in the national reimbursement drug list

The drugs captopril and enalapril are adopted in Categories A of the China National Reimbursement Drug List (NRDL), and without payment restrictions, therefore, could score 3 points. Other ACEIs are adopted in Categories B of the China NRDL with payment restrictions, therefore, score 2 points.

### 4.5.2 Essential Drug List

Captopril and enalapril are listed in the "National Essential Drug List" without a "Δ" symbol, therefore, receive 3 points; the other 5 ACEIs are not listed in the "National Essential Drug List" and receive 1 point.

### 4.5.3 Storage conditions

Captopril requires storage at room temperature, away from light or shaded, and receives 2.5 points, while fosinopril requires storage in a cool place, away from light or shaded, and receives 1.5 points. The other ACE inhibitors only require storage at room temperature and do not require protection from light, and therefore receive 3 points.

### 4.5.4 Expiration date

All ACEI drugs evaluated in this consensus have an Expiration date between 24 and 36 months, therefore, they all receive 2 points.

### 4.5.5 Global market situation

Ramipril and Fosinopril are not marketed in Japan, and Imidapril is not marketed in the United States. Therefore, they all score 2 points. Captopril, Benazepril, Enalapril, and Perindopril are marketed in the United States, Europe, and Japan, so they all score 3 points.

### 4.5.6 Production company rating

All evaluated drugs are produced by pharmaceutical companies listed among the

top 50 in global sales (according to Pharma Exec)<sup>[15]</sup>, therefore they are awarded 3 points. Specific scoring for other attributes can be found in Table 8.

**Table 8 Other features evaluation for ACEIs**

Other features (Up to 18 points)	Scoring criteria (Up to points)	Captopril	Benzapril	Enalapril	Perindopril	Ramipril	Fosinopril	Imidapril
Inclusion in the national reimbursement drug list (3)	Drug was selected into Categories A of the China National Reimbursement Drug List (NRDL), and without payment restrictions. (3)	3		3				
	Drug was selected into Categories A of the China NRDL, but with payment restrictions. (2.5)							
	Drug was selected into Categories B of the China NRDL, and without payment restrictions. (2)		2		2	2	2	2
	Drug was selected into Categories B of the China NRDL, but with payment restrictions. (1.5)							
	Not selected into the China NRDL. (1)							
Inclusion in the national essential drug list (3)	Drug is in the national essential drug list, without symbol “△”. (3)	3		3				
	Drug is in the national essential drug list, with a symbol “△” score 2 points. (2)							
	Drug is not a national essential drug. (1)		1		1	1	1	1
Storage conditions (3)	Stored in room temperature. (3)		3	3	3	3		3
	Stored in room temperature and need to away from light or in a light-resistant container. (2.5)	2.5						
	Stored in cool place. (2)							
	Stored in cool place score and away from light or in a light-resistant container. (1.5)						1.5	
	Stored in a refrigerated or frozen condition. (1)							
Expiration date (3)	Expiration date >36 months. (3)							
	Expiration date ranking 24~36 months. (2)	2	2	2	2	2	2	2

	Expiration date <24 months. (1)							
Global market approval status (3)	Already marketed in the United States, Europe, and Japan (3)	3	3	3	3			
	Already marketed in the United States, Europe, or Japan. (2)					2	2	2
	Not marketed in the United States, Europe, and Japan. (1)							
Manufacturing company rating (3)	Top 50 pharmaceutical companies (according to Pharmaceutical Executive, United States). (3)	3	3	3	3	3	3	3
	Top 100 enterprises of Ministry of Industry and Information Technology of the People's Republic of China. (2)							
	Other companies score 1 point. (1)							
<b>Total</b>		<b>16.5</b>	<b>14</b>	<b>17</b>	<b>14</b>	<b>13</b>	<b>11.5</b>	<b>13</b>

## 5. Application of the comprehensive evaluation results

The consensus is based on the evaluation system of "Quick Guidelines for Drug Evaluation and Selection in Chinese Medical Institutions" and combines the clinical application characteristics of ACE inhibitors to establish a scientific, objective, and quantitative comprehensive evaluation method. The aim is to provide reference for medical institutions to carry out rapid comprehensive evaluation of ACE inhibitors and provide a basis for drug selection and optimization of drug formulary.

The drugs evaluated in this consensus are seven original ACE inhibitors widely marketed in China. The evaluation results show that enalapril scored the highest among the seven ACE inhibitors with a score of 80.3, mainly due to its outstanding advantages in terms of economy, pharmaceutical characteristics, and other attributes. The other ACE inhibitors were ranked in the following order: ramipril, captopril, perindopril, fosinopril, benazepril, and imidapril. The overall score results can be divided into three levels: ramipril, captopril, perindopril, and enalapril were ranked in the first tier, fosinopril and benazepril were ranked in the second tier, and imidapril and other ACE inhibitors had a significant difference in scores and were ranked in the third tier.

When introducing new drugs, the evaluation results can be used to determine whether to introduce them. When adjusting drugs, if medical institutions have multiple ACE inhibitors ( $\geq 3$  types), drug selection can be based on the score

ranking. Drugs with lower scores are recommended to be temporarily retained or removed. Please refer to Table 9 for specific scoring information.

It should be noted that the evaluation results of this consensus are only for reference in drug selection and cannot be used as guidance for clinical medication. Most ACE inhibitors have clear research results in terms of efficacy and safety. During the evaluation process of this consensus, we adjusted the weights of the evaluation dimensions, and the results are no longer greatly affected by economic and other attributes. However, drug evaluation work needs to be continuously updated and dynamically adjusted, incorporating new evidence-based medicine, new medical insurance policies, price information, etc., to reflect drug characteristics in real-time. In addition, for subsequent generic drugs or newly introduced ACE inhibitors in China, this evaluation standard can be used as a reference to improve the documentation and evidence of various attributes, for subsequent medical institutions to conduct more scientific, objective, and realistic rapid comprehensive evaluation and selection of drugs.

**Table 9 Scoring Results of the ACEIs**

Evaluation Dimension	Enalapril	Ramipril	Captopril	Perindopril	Fosinopril	Benazepril	Imidapril
Pharmaceutical properties	20.8	23.8	21.8	22.8	21.8	20.8	20.8
Efficacy	21	23	21.5	21.5	19.5	17.5	15.5
Safety	10.5	9	10	10	12	11.5	9
Economy	11	9	8	9	11	8	9
Other features	17	13	16.5	14	11.5	14	13
<b>Total</b>	<b>80.3</b>	<b>77.8</b>	<b>77.8</b>	<b>77.3</b>	<b>75.8</b>	<b>71.8</b>	<b>67.3</b>

The evaluation results of this consensus are not set in stone, as factors such as economic considerations, healthcare policies, essential drug lists, and market information are all dynamic indicators. As clinical research evidence on drugs continues to accumulate, guidelines are updated, and changes occur in drug pricing, essential drug lists, and market information, the evaluation scores may change accordingly. To facilitate the application of the evaluation results, we have prepared

a comprehensive summary of the drugs evaluated in this consensus, outlining their strengths and weaknesses for decision-makers to reference.

Enalapril is a national essential medicine. It needs to be metabolized into enalaprilat in the body to take effect, with a half-life of about 11 hours and an average peak valley ratio of >50%. Some patients need to take it twice a day, and compliance should be noted in such patients. It is minimally affected by food and can be taken before or after meals. It has a wide range of clinical indications and is used not only for hypertension and heart failure, but also for preventing events in patients with left ventricular dysfunction. The safety data for enalapril in pediatric patients is sufficient, and it can be used in patients from 1 month to 16 years of age. Like other ACE inhibitors, it is contraindicated in pregnant women, and caution should be exercised when used in lactating women due to the small amount of enalapril and enalaprilat secreted in breast milk. The incidence of dry cough is relatively high compared to other ACE inhibitors. The dosage needs to be adjusted in patients with liver and kidney function abnormalities, and it should be used with caution.

Ramipril needs to be metabolized into ramiprilat in the body to take effect, with a half-life of about 13-17 hours and an average peak valley ratio of about 50-63%. It can be taken once a day, and it is minimally affected by food and can be taken before or after meals. When using it, the tablet should be swallowed whole and not crushed. The incidence of dry cough with this drug is relatively high among ACE inhibitors. It has the most approved indications domestically and can be used in children and adolescents. Like other ACE inhibitors, it is contraindicated in pregnant women and not recommended for lactating women. The dosage needs to be adjusted in patients with severe liver and kidney function abnormalities.

Captopril is a national essential medicine and the first ACE inhibitor used clinically. It is the only ACE inhibitor evaluated in this consensus that can take effect without being converted into a metabolite. Its absorption is greatly affected by food and needs to be taken before meals. It has the shortest half-life of only 2 hours, with an average peak valley ratio of about 25%, and needs to be taken 2-3 times a day. Due to its rapid action, it is often used sublingually for hypertensive emergencies. However, when used for chronic diseases that require long-term medication, attention should be paid to medication compliance. In addition to hypertension and heart failure, captopril can also be used for diabetic nephropathy in type 1 diabetes patients and for preventing cardiovascular events after a heart attack. The incidence of dry cough with this drug is relatively high. Its structure contains a thiol group,

which can cause taste disorders, rashes, and decreased granulocyte count, which are more common adverse reactions than other ACE inhibitors. This drug can be used in pediatric patients, is contraindicated in pregnant women, and can be used with caution in lactating women. Dosage adjustment is necessary in patients with liver and kidney function abnormalities, and caution should be exercised when using this drug. It is also used as a diagnostic drug in the captopril test for the diagnosis of primary aldosteronism.

Perindopril needs to be metabolized into perindoprilat in the body to exert its effect. The average trough-to-peak ratio is about 35%, but the half-life of the active metabolite is approximately 30 hours, so it is usually taken once a day. Food reduces its bioavailability, so it should be taken before meals. The incidence of dry cough with this medication is relatively low among ACE inhibitors. In addition to hypertension and heart failure, there is also clinical evidence of benefit in stable angina patients. It is not recommended for use in pediatric patients due to a lack of safety and efficacy data. Like other ACE inhibitors, it is contraindicated in pregnant women, and not recommended for use in breastfeeding women. It usually does not need to be adjusted in patients with abnormal liver function, but the dose should be reduced in those with abnormal kidney function.

Fosinopril needs to be converted into Fosinoprilat in the body to exert its effects, with a half-life of about 12 hours and an average peak-to-trough ratio of 64%. Its absorption is not affected by food. This drug has a relatively low incidence of dry cough among ACE inhibitors. There is a recommended dosage for pediatric patients over 6 years old. Like other ACE inhibitors, it is contraindicated in pregnant and lactating women. This drug is metabolized by both the liver and kidney, and patients with liver or kidney dysfunction can compensate through alternative pathways, so there is no need to adjust the dosage in patients with liver or kidney dysfunction.

Benazepril needs to be metabolized into Benazeprilat in the body to exert its effects, with a half-life of about 11 hours and an average peak-to-trough ratio of about 40%. Some patients still need to take it twice a day, so compliance should be taken into account. Its absorption is minimally affected by food, and it can be taken before or after meals. This drug has a relatively low incidence of dry cough among ACE inhibitors, and its incidence of adverse reactions such as taste disorders and granulocytopenia is much lower than that of Captopril. In addition to hypertension and heart failure, there is also a lot of evidence-based evidence for delaying the



progression of kidney disease in Chinese populations. Benazepril should be used with caution in pediatric patients, contraindicated in pregnant women, and can be cautiously used in lactating women. There is usually no need to adjust the dosage in patients with liver dysfunction, but it is necessary to reduce the dosage in patients with renal dysfunction.

Imidapril needs to be metabolized into its active form, imidaprilat, in the body. Its half-life is approximately 8 hours, and its average peak concentration can reach 84%. It is usually taken once a day, and is minimally affected by food, so it can be taken before or after meals. Compared to other ACE inhibitors, this drug has a relatively low incidence of dry cough. It is only approved for the treatment of hypertension in China and should not be used in pediatric patients. Like other ACE inhibitors, it is contraindicated in pregnant women and should be used with caution in breastfeeding women. The dosage should be adjusted in patients with impaired liver or kidney function and should be used with caution in such patients.

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### **Prescription Information (Chinese version)**

卡托普利片（商品名：开博通），修改日期：2017年4月10日。

贝那普利片（商品名：洛汀新），修改日期：2020年04月29日。

依那普利片（商品名：悦宁定），修改日期：2021年2月2日。

培哌普利叔丁胺片（商品名：雅施达），修改日期：2020年12月30日。

雷米普利片（商品名：瑞泰），修改日期：2021年4月27日。

福辛普利片（商品名：蒙诺），修改日期：2021 年 11 月 8 日。

咪达普利片（商品名：达爽），修改日期：2021 年 12 月 24 日。

### **Prescription Information and SmPC:**

CAPTOPRIL- captopril tablet, Revised: 4/2018

LOTENSIN- benazepril hydrochloride tablet, Revised: 1/2019

ENALAPRIL MALEATE- enalapril maleate tablet, Revised: 2/2019

Perindopril (perindopril tert-butylamine), SmPC, Revised: 1/2022

Tritace (ramipril), SmPC, Revised: 6/2021

Fosinopril Sodium Tablets, SmPC, Revised: 1/2021

Tanatril (Imidapril) tablets, SmPC, Revised: 1/2022

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