Technology Guidance

Review of cancer drugs

for prostate cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Degarelix 80 mg and 120 mg injections;
- ✓ Enzalutamide 40 mg capsule; and
- ✓ Olaparib 100 mg and 150 mg tablets

for treating prostate cancer in line with specific clinical criteria.

Subsidy status

Degarelix 80 mg and 120 mg injections are recommended for inclusion on the Medication Assistance Fund (MAF) for treating advanced hormone-dependent prostate cancer with effect from 4 January 2022.

Enzalutamide 40 mg capsule, in combination with androgen deprivation therapy (ADT) is recommended for inclusion on MAF for treating:

- high-risk non-metastatic castration-resistant prostate cancer (nmCRPC);
- metastatic hormone-sensitive prostate cancer (mHSPC); and
- metastatic castration-resistant prostate cancer (mCRPC).

Olaparib 100 mg and 150 mg tablets are recommended for inclusion on MAF for treating patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene BRCA1/2 and/or ATM-mutations (germline and/or somatic) whose disease has progressed following prior treatment with abiraterone or a second-generation anti-androgen. Androgen deprivation therapy (ADT) should be continued.

MAF assistance for enzalutamide and olaparib will be implemented from 1 September 2022.

Updated: 19 December 2022

MAF assistance **does not** apply to apalutamide 60 mg tablet, darolutamide 300 mg tablet, olaparib 50 mg capsule or cabazitaxel 60 mg/1.5 mL injection for the treatment of prostate cancer.

Clinical indications, subsidy class and MediShield Life claim limits for all drugs included in the evaluation are provided in the Annex.

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of second-generation anti-androgens (apalutamide, darolutamide, enzalutamide), cabazitaxel, degarelix and olaparib for treating prostate cancer. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for all drugs was considered in line with their registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of the drugs under evaluation and provided clinical advice on their appropriate and effective use based on the available clinical evidence.

1.2. Estramustine was outside the scope of the evaluation following advice from local clinical experts and ODS members who considered that there was no clinical need to consider this treatment for subsidy. Olaparib 50 mg capsule was excluded from evaluation as the manufacturer confirmed that it is being discontinued and replaced by 100 mg and 150 mg tablets.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1. The Committee noted that there are approximately 970 cases of prostate cancer diagnosed each year in Singapore and there was a high clinical need to consider treatments for subsidy to improve affordability and ensure appropriate patient care.

2.2. The Committee acknowledged that local clinical practice to treat prostate cancer is generally consistent with international guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO), as well as local guidelines from the Singapore Cancer Network (SCAN).

2.3. The Committee heard that androgen deprivation therapy (ADT) including leuprorelin, goserelin and degarelix, has long been the standard of care for treating prostate cancer and is continued throughout the treatment pathway. They noted that leuprorelin and goserelin are already listed on MAF for treating prostate cancer, therefore, there is no therapeutic gap in the MOH List of Subsidised Drugs.

2.4. The Committee noted that cabazitaxel is used in local practice for men with metastatic castrate-resistant prostate cancer (mCRPC) whose disease has progressed after a docetaxel-containing regimen.

2.5. The Committee acknowledged that prostate cancer has a variable disease course that progresses from hormone-sensitive to castrate-resistant prostate cancer, and from localised to metastatic disease despite ADT. Treatment of prostate cancer is evolving with other therapies, such as abiraterone and second-generation anti-androgens being used earlier in the treatment pathway.

2.6. The Committee discussed differences in the HSA-approved indications of the anti-androgen therapies and noted that apalutamide and enzalutamide are approved for treating men with metastatic hormone-sensitive prostate cancer (mHSPC), whereas only enzalutamide is approved for treating men with mCRPC. Apalutamide, darolutamide and enzalutamide are all approved for treating men with non-metastatic castrate-resistant prostate cancer (nmCRPC). While local experts noted that generic abiraterone is already included in the MOH List of Subsidised Drugs and can also be used to treat mHSPC and mCRPC, they suggested that apalutamide or enzalutamide are useful as a steroid-sparing treatment option for men who cannot tolerate prednisolone which is given in combination with abiraterone. However, they cautioned that it is difficult to limit and define the population which is likely to be contraindicated for abiraterone or steroid use in local practice and advised the Committee that a subsidy recommendation for this specific subgroup of patients would not be practical to implement. The Committee acknowledged there was an unmet clinical need for anti-androgen therapy for nmCRPC, however, there are very few patients diagnosed each year with this condition in Singapore.

2.7. The Committee noted that olaparib is typically reserved for men with mCRPC and homologous recombination repair (HRR) gene BRCA1/2 and/or ATM-mutations whose disease has progressed following prior treatment with abiraterone or a second-generation anti-androgen. They acknowledged that there is currently no subsidised biomarker-directed therapy for patients with HRR gene mutations in prostate cancer, representing a therapeutic gap.

Clinical effectiveness and safety

3.1. Cabazitaxel and degarelix

The Committee acknowledged that available clinical evidence for cabazitaxel and degarelix has consistently shown clinical benefits for patients with prostate cancer, and both treatments are well established in clinical practice.

3.2. Second-generation anti-androgens (apalutamide, darolutamide and enzalutamide)

The Committee reviewed the available evidence for apalutamide, darolutamide and enzalutamide for treating nmCRPC. All trials showed overall survival (OS) and metastasis-free survival (MFS) benefit for the anti-androgens compared with placebo. Given the lack of head-to-head trials comparing the drugs with each other, there was no evidence to support the superiority of any drug over another. The Committee heard that local experts considered the anti-androgens were clinically comparable in efficacy and safety.

3.3. In the mHSPC setting, the Committee heard that data from trials for apalutamide and enzalutamide were immature and median OS and progression-free survival (PFS) were not reached at the time of the evaluation. Interim analyses showed statistically significant improvements in PFS for both drugs compared to placebo. The Committee also acknowledged results from network meta-analyses considered by CADTH (Canada) which suggested that apalutamide and enzalutamide were comparable in efficacy and safety.

3.4. The Committee reviewed the available evidence for enzalutamide for treating men with mCRPC in whom chemotherapy is not yet clinically indicated, and whose disease has progressed on or after docetaxel therapy. Evidence showed OS and PFS benefits for enzalutamide compared with placebo. While there were no head-to-head trials available comparing enzalutamide with abiraterone, the Committee noted that overseas HTA agencies considered enzalutamide was non-inferior to abiraterone in terms of comparative effectiveness and safety for treating mCRPC.

3.5. Olaparib

The Committee reviewed the available evidence for olaparib that showed statistically OS and PFS gains with olaparib compared to enzalutamide or abiraterone in patients with at least one alteration in BRCA1, BRCA2, or ATM. However, the evidence showed no survival benefit in patients with other gene mutations (BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L). The Committee noted that findings were consistent with recommendations from CADTH (Canada), which had also considered olaparib was effective only for patients with mutations in the HRR gene BRCA1/2 or ATM. The Committee heard that local experts considered olaparib was generally well tolerated.

Cost effectiveness

4.1. All manufacturers were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration. In the absence of a local cost-effectiveness analysis of treatments for prostate cancer, the Committee reviewed results from overseas HTA agencies (where available) and agreed that they were likely to be generalisable to the local context.

4.2. Cabazitaxel and degarelix

The Committee acknowledged that the price offered by the manufacturer for degarelix was comparable to prices of leuprorelin and goserelin, and agreed that an MAF listing was appropriate to provide an alternative subsidised ADT for patients to improve affordability. The Committee noted that the price proposed for cabazitaxel was considerably higher than its prices in overseas reference jurisdictions, and concluded that it was unlikely that cabazitaxel would be cost effective in the local context.

4.3. Second-generation anti-androgens (apalutamide, darolutamide and enzalutamide)

In the nmCRPC setting, the Committee agreed that a cost-minimisation approach was appropriate to select the least expensive second-generation anti-androgen for subsidy in view of their comparable efficacy and safety. The Committee acknowledged that the price proposed by the manufacturer for darolutamide was higher than the prices offered for enzalutamide and apalutamide.

4.4. The Committee acknowledged that enzalutamide was recommended by PBAC (Australia) and CADTH (Canada) on a cost-minimisation basis with abiraterone for treating men with mCRPC. Given the availability of generic abiraterone, the Committee noted that apalutamide or enzalutamide were unlikely to be cost effective in the local context without a price volume agreement (PVA) in place to reduce uncertainty surrounding the overall budget impact and improve cost-effectiveness. The Committee heard that while apalutamide was competitively priced, the manufacturer did not agree to a PVA; however, the manufacturer of enzalutamide did and also proposed a price which was comparable to overseas reference prices; therefore, the Committee agreed that a MAF listing for enzalutamide was appropriate to provide an affordable treatment option for patients who are unable to receive abiraterone.

4.5. Olaparib

The Committee heard that overseas reference HTA agencies had not yet made subsidy recommendations for olaparib at the time of evaluation. In view of acceptable cost-effectiveness at the proposed price and a PVA agreed with the manufacturer to reduce uncertainty in the overall budget impact, the Committee concluded that a MAF listing for olaparib was appropriate.

Estimated annual technology cost

5.1. Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual cost impact for each drug in the first year of listing on MAF for treating prostate cancer was estimated to be:

- Degarelix (MAF): less than SG$1 million;
- Enzalutamide (MAF): between SG$1 million to less than SG$3 million; and
- Olaparib (MAF): less than SG$1 million.

Additional considerations

6.1. The Committee acknowledged that, contingent on subsidy listing, the manufacturer of olaparib had agreed to implement a patient assistance programme (PAP) for eligible patients which would provide further savings to patients in addition to MAF financial assistance.

Recommendations

7.1. Cabazitaxel and degarelix

The Committee recommended degarelix 80 mg and 120 mg injections be listed on MAF for patients with advanced hormone-dependent prostate cancer in view of acceptable cost effectiveness compared with other ADTs.

7.2. Cabazitaxel was not recommended for listing on MAF due to unacceptable cost effectiveness at the price proposed by the manufacturer.

7.3. Second-generation anti-androgens (apalutamide, darolutamide and enzalutamide)

Based on available evidence, the Committee recommended enzalutamide 40 mg capsule be listed on MAF for men with high-risk nmCRPC, mHSPC, or mCRPC, in view of acceptable cost effectiveness with a PVA agreed with the manufacturer to reduce uncertainty in the overall budget impact and improve cost-effectiveness.

7.4. At the price proposed by the manufacturer, darolutamide was not recommended for listing on MAF due to unacceptable cost effectiveness compared to enzalutamide. Given no agreement was reached for establishing a PVA to reduce uncertainty surrounding the overall budget impact and improve cost-effectiveness, apalutamide was not recommended for listing on MAF.

7.5. Olaparib

The Committee recommended olaparib 100 mg and 150 mg tablets be listed on MAF for patients with mCRPC and homologous recombination repair gene BRCA1/2 and/or ATM-mutations (germline and/or somatic) whose disease has progressed following prior treatment with abiraterone or a second-generation anti-androgen in view of acceptable cost-effectiveness at the proposed prices and a PVA agreed with the manufacturer to reduce the uncertainty in the overall budget impact.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Second-generation anti-androgen			
Enzalutamide 40 mg capsule	In combination with androgen deprivation therapy (ADT) for treating patients with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). ‡	MAF (1 Sep 2022)	$400 (1 Sep 2022)
	In combination with androgen deprivation therapy (ADT) for treating patients with metastatic hormone-sensitive prostate cancer (mHSPC). ‡		
	In combination with androgen deprivation therapy (ADT) for treating patients with metastatic castration-resistant prostate cancer (mCRPC). ‡		
Apalutamide 60 mg tablet	In combination with androgen deprivation therapy (ADT) for treating patients with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). ‡	Not recommended for subsidy	$400 (1 Sep 2022)
	In combination with androgen deprivation therapy (ADT) for treating patients with metastatic hormone-sensitive prostate cancer (mHSPC). ‡		
Darolutamide 300 mg tablet	In combination with androgen deprivation therapy (ADT) for treating patients with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). ‡	Not recommended for subsidy	$400 (1 Sep 2022)
Other therapies			
Degarelix 80 mg & 120 mg injections	Treatment of patients with advanced hormone-dependent prostate cancer.	MAF (4 Jan 2022)	$200 (1 Sep 2022)
Olaparib 100 mg & 150 mg tablets	Treatment of patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene BRCA1/2 and/or ATM-mutations (germline and/or somatic) whose disease has progressed following prior treatment with abiraterone or a second-generation anti-androgen. Androgen deprivation therapy (ADT) should be continued. ‡	MAF (1 Sep 2022)	$1600 (1 Sep 2022)

Cabazitaxel 60 mg/1.5 mL injection	Cabazitaxel in combination with prednisolone: for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen. Androgen deprivation therapy (ADT) should be continued. ‡	Not recommended for subsidy	$1400 (1 Sep 2022)

Abbreviations: MAF, Medication Assistance Fund; ‡ revised clinical indication with effect from 1 Feb 2023.

VERSION HISTORY

Review of cancer drugs for prostate cancer

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

Publication of guidance

Date of Publication 4 Jan 2022

Guidance updated with the following changes:

- revised clinical indication for enzalutamide, apalutamide, darolutamide, olaparib and cabazitaxel

Date of Publication 19 Dec 2022

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 16 March 2021, 2 July 2021 and 20 September 2022. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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