After being heard on 18 July 2012, the opinion of the Transparency Committee was adopted on 5 September 2012.

COMBODART 0.5 mg/0.4 mg, hard capsules
- Vial (HDPE) of 30 hard capsules, B/1 (CIP: 389 339-8)
- Vial (HDPE) of 90 hard capsules, B/1 (CIP: 498 790-2)

Applicant: GLAXOSMITHKLINE

Fixed-dose combination of dutasteride and tamsulosin (hydrochloride)

ATC code: G04CA52

List I

Date of Marketing Authorisation (decentralised European procedure): 28 June 2010
(Rapporteur country: Germany)

Reason for request: Inclusion on the list of medicines refundable by National Heath Insurance and approved for hospital use.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients
Fixed-dose combination of dutasteride and tamsulosin.
Each hard capsule contains sustained-release microgranules of 0.4 mg tamsulosin hydrochloride (equivalent to 0.367 mg of tamsulosin) and one soft gelatin capsule of 0.5 mg dutasteride.

1.2. Indications
“- Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).
- Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.”

1.3. Dosage
Adults (including elderly patients): One hard capsule per day approximately 30 minutes after the same meal.

“Where appropriate, COMBODART may be used to substitute concomitant dutasteride and tamsulosin hydrochloride in existing dual therapy to simplify treatment.
Where clinically appropriate, direct change from dutasteride or tamsulosin hydrochloride monotherapy to COMBODART may be considered.”

Renal impairment: “The effect of renal impairment on dutasteride-tamsulosin pharmacokinetics has not been studied. No adjustment in dosage is anticipated for patients with renal impairment.”
The SmPC specifies that COMBODART should be used with caution in “severely renally impaired patients (creatinine clearance of less than 10 ml/min).”

Hepatic impairment: “The effect of hepatic impairment on dutasteride-tamsulosin pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of COMBODART is contraindicated.”

History of orthostatic hypotension: COMBODART is contraindicated due to the presence of the alpha blocker (tamsulosin).

Method and route of administration
“The capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa.”
The SmPC specifies that “dutasteride is absorbed through the skin, therefore, women, children and adolescents must avoid contact with leaking capsules. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.”
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

G:  Genitourinary system and sex hormones
G04: Urologicals
G04C: Drugs used in benign prostatic hypertrophy
G04CA: Alpha-adrenoceptor antagonists (alpha blockers)
G04CA52: Tamsulosin and dutasteride

2.2. Medicines in the same therapeutic category

Comparator medicines:

2.2.1. Separate dosing with each of COMBODART’s two active ingredients:

- Tamsulosin hydrochloride-based proprietary medicinal products:
  JOSIR LP 0.4 mg/hard capsule; OMIX 0.4 mg/SR hard capsule, and their generics.
  MECIR 0.4 mg/SR tablet; OMEXEL 0.4 mg/SR tablet.

- Dutasteride-based proprietary medicinal product: AVODART 0.5 mg/soft capsule.

2.2.2. Separate dosing with another alpha blocker\(^1\) (alfuzosin, doxazosin, silodosin or terazosin) and/or the other 5-alpha reductase inhibitor (finasteride):

- Alfuzosin-based proprietary medicinal products: URION 2.5 mg/tablet; XATRAL 2.5 mg/tablet; XATRAL LP 10 mg/tablet and their generics.

- Doxazosin-based proprietary medicinal products: ZOXAN LP 4 mg/SR tablet and its generics; ZOXAN LP 8 mg/SR tablet.

- Finasteride-based proprietary medicinal products: CHIBRO-PROSCAR 5 mg/tablet and its generics.

- Silodosin-based proprietary medicinal products: SILODYX 4 mg hard capsule/SILODYX 8 mg hard capsule and UROREC 4 mg hard capsule/UROREC 8 mg hard capsule.

- Terazosin-based proprietary medicinal products: DYSALFA 1 mg/tablet and 5 mg/tablet; HYTRIN 1 mg/tablet and 5 mg/tablet and their generics.

2.3. Medicines with a similar therapeutic aim

In the treatment of moderate symptoms of BPH:

- PERMIXON 160 mg (serenoa repens: lipidosterolic extract composed of free and/or esterified fatty acids (97%) and an unsaponifiable fraction (3%)) and its generics.

- TADENAN (Pygeum africanum Hook.f. extract) 50 mg soft capsules

These medicines are all indicated in the treatment of functional BPH symptoms.

The proprietary medicinal products containing a 5-ARI (AVODART and CHIBRO-PROSCAR) are also indicated to “reduction the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe BPH symptoms”.

Furthermore, the alfuzosin-based proprietary medicinal products (URION and XATRAL) are indicated as “adjuvant therapy to bladder catheterisation in acute urinary retention related to benign prostatic hyperplasia (10 mg dosage only)”. All these medicines have a “moderate” actual benefit with an efficacy/adverse effects ratio qualified as “modest”.

The SABAL SERRULATA COMPOSE, oral solution\(^2\) proprietary medicinal product is indicated and refundable for “functional disorders related to benign prostatic hyperplasia”.

\(^1\) The prazosin-based proprietary medicinal products, MINIPRESS 1 mg tablet and MINIPRESS 5 mg tablet, have an insufficient AB.
3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Bioequivalence has been established between the fixed-dose dutasteride-tamsulosin combination (with the COMBODART and DUODART proprietary medicinal products) and concomitant administration of each component taken separately (see the SmPC).

No therapeutic clinical trial has been conducted with the COMBODART fixed-dose combination.

The clinical benefit in taking dutasteride and tamsulosin concomitantly compared with taking either dutasteride or tamsulosin (monotherapies) was evaluated in a phase IIIb trial (ARI40005, the so-called “CombAT trial”) involving 4,844 benign prostatic hyperplasia (BPH) patients considered at risk of progression.

The objective was to establish the superiority of taking dutasteride and tamsulosin concomitantly versus taking each as monotherapy in improving BPH symptoms after 2 years of treatment and in reducing complications after 4 years of treatment.

Methodology: This was a randomised, double-blind study with three parallel groups. After receiving a placebo for 4 weeks, the patients were randomised (ratio 1:1:1) to receive a daily oral dose 30 minutes after breakfast of:
- the combination of dutasteride 0.5 mg/day + tamsulosin 0.4 mg/day (N = 1610)
- dutasteride 0.5 mg/day and a tamsulosin placebo (N = 1623)
- tamsulosin 0.4 mg/day and a dutasteride placebo (N = 1611).

The study subjects were at least 50 years of age and had benign prostatic hyperplasia (BPH) with symptoms of moderate to severe intensity (an IPSS score ≥ 12 and a maximum urine flow rate of 5 to 15 ml/s). These patients were considered at risk of progression because they had a prostate volume of more than 30 ml and a total serum PSA level of 1.5 to 10 ng/ml.

Two primary efficacy endpoints were selected:
- Reduction in BPH symptoms, assessed by the mean reduction in IPSS score after 2 years of treatment
- Prolongation of the time to first onset of acute urinary retention (AUR) or time to BPH-related surgery after 4 years of treatment.

The secondary efficacy endpoints were a modification at after years in the:
- IPSS score (variation and percentage of responders) compared with the initial value on inclusion
- Clinical progression, defined as a composite endpoint including an IPSS decrease of ≥ 4 points, the occurrence of BPH-related AUR, incontinence, urinary infection and renal impairment
- Maximum urine flow rate (Qmax)
- Prostate volume
- Quality of life using two questionnaires (IPSS-Q8 and BPH Impact Index evaluating physical discomfort, anxiety, level of impairment and effect on daily activities).

2 This is a homeopathic medicine containing: sabal serrulata (H) 3 CH, picricum acidum (H) 3 CH, baryta carbonica (H) 3 CH, berberis vulgaris (H) 3 CH, thuja occidentalis (H) 3 CH, anemone pulsatilla (H) 3 CH, conium maculatum (H) 3 CH, thlaspi bursa pastoris (H) 3 DH.
3 The significance threshold of the bilateral statistical tests was set at 0.01 (and not 0.05) to take the three statistical tests performed into consideration. The efficacy analyses were on an intention-to-treat basis.
4 The responders were defined by an improvement in IPSS score at four years of at least 3 points or 25% compared with the inclusion score.
5 Question 8 appended to the IPSS score.
This trial included two co-primary endpoints, which were taken into consideration when calculating the number of subjects and for which sufficient power (> 90% for each endpoint) had been planned. This calculation was also based on a study withdrawal rate of 25% at 2 years and 35% at 4 years.

The inclusion of 1500 patients per treatment arm was to enable a power:
- of 94% to conclude that the combination was superior to tamsulosin alone with respect to the analyses of complications after 4 years (knowing that dutasteride alone probably could account for this effect, no significant difference was expected between the combination and dutasteride)
- of 91% to conclude that the combination was superior to the two monotherapy arms with respect to the IPSS analyses after 2 years, since a restrictive significance threshold (0.01 versus the standard 0.05) had been set to strengthen the reliability of the observed differences (two tests were carried out).

Efficacy results
The study was carried out from November 2003 to January 2007 for the two-year analysis and until January 2009 for the 4-year analysis.

Of the 4844 men randomised to one of three treatment groups, 3822 (79%) came to the 24-month visit. There were 232 (4.8%) patients included in France. A total of 3195 patients (66%) remained in the study to the end of the 48-month study duration with a higher rate of study withdrawal in the tamsulosin group (39%) than in the combination (31%) and dutasteride (33%) groups.

The characteristics of the patients on inclusion (Table 1) were comparable for the three arms: the patients were aged 66.1 years on average and had been experiencing symptoms (LUTS) for 5.4 years on average. In addition, 71% of included patients had moderate BPH symptoms with an IPSS score of less than 20. It should be noted that 51% of patients were alpha blocker-naïve and 39% were naïve for all medicinal treatments.

Table 1: Characteristics of patients on inclusion

<table>
<thead>
<tr>
<th></th>
<th>Combination (N = 1610)</th>
<th>Dutasteride (N = 1623)</th>
<th>Tamsulosin (N = 1611)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.0 (7.0)**</td>
<td>66.0 (7.0)</td>
<td>66.2 (7.0)</td>
</tr>
<tr>
<td>Total IPSS (points)</td>
<td>16.6 (6.4)</td>
<td>16.4 (6.0)</td>
<td>16.4 (6.1)</td>
</tr>
<tr>
<td>History of LUTS (years)</td>
<td>5.4 (5.1)</td>
<td>5.3 (4.7)</td>
<td>5.4 (4.8)</td>
</tr>
<tr>
<td>Total prostate volume (ml)</td>
<td>54.7 (23.5)</td>
<td>54.6 (23.0)</td>
<td>55.8 (24.2)</td>
</tr>
<tr>
<td>Median (ml)</td>
<td>48.9</td>
<td>48.4</td>
<td>49.6</td>
</tr>
<tr>
<td>Transition zone volume (ml)*</td>
<td>27.7 (20.2)</td>
<td>30.3 (21.0)</td>
<td>30.5 (24.5)</td>
</tr>
<tr>
<td>Serum PSA (ng/ml)</td>
<td>4.0 (2.1)</td>
<td>3.9 (2.1)</td>
<td>4.0 (2.1)</td>
</tr>
<tr>
<td>Qmax (ml/s)</td>
<td>10.9 (3.6)</td>
<td>10.6 (3.6)</td>
<td>10.7 (3.7)</td>
</tr>
<tr>
<td>Post-void residual volume (mL)</td>
<td>68.1 (66.0)</td>
<td>67.4 (63.5)</td>
<td>67.7 (65.1)</td>
</tr>
<tr>
<td>Sexually active</td>
<td>73% (1176/1610)</td>
<td>73% (1189/1622)</td>
<td>72% (1164/1610)</td>
</tr>
<tr>
<td>Prior treatment with alpha blocker</td>
<td>50% (805/1608)</td>
<td>51% (820/1622)</td>
<td>51% (819/1611)</td>
</tr>
<tr>
<td>Prior treatment with 5-ARI</td>
<td>11% (171/1531)</td>
<td>12% (188/1567)</td>
<td>11% (172/1560)</td>
</tr>
<tr>
<td>Prior treatment with plant extracts</td>
<td>20% (328/1609)</td>
<td>18% (297/1622)</td>
<td>20% (321/1611)</td>
</tr>
</tbody>
</table>

* Sub-group of 656 men  
**The data is presented as a mean (standard deviation) or percentage (number/N).
- **Efficacy results:**

Primary efficacy endpoints:

- After 2 years of treatment, the adjusted difference in the mean IPSS variation was -1.3 points [-1.69; -0.86], p<0.001 between the combination and dutasteride arms and -1.8 points [-2.23; -1.40], p<0.001 between the combination and tamsulosin arms.

- After 4 years of treatment, the time to onset of an event (AUR episode or BPH-related surgery) was longer (p<0.001) in the arm receiving the combination than in the arm receiving tamsulosin. After 8 months, the tamsulosin treatment group had a cumulative incidence of AUR episodes or BPH-related surgery during the study that was greater than for the combination and dutasteride arms, and the value of this difference increased over time until the 48th month (see Figure 1). There was no demonstrated difference between the combination and dutasteride arms on this endpoint.

Figure 1: Kaplan-Meier curves for time to onset of the first episode of acute urinary retention or BPH-related surgery and number of events per arm for each assessment year compared with the analysis population (Primary endpoint – LOCF).

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Combination</th>
<th>Dutasteride</th>
<th>Tamsulosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29</td>
<td>43</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>1610</td>
<td>1457</td>
<td>1347</td>
</tr>
<tr>
<td>24</td>
<td>58</td>
<td>1274</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The percentage of patients who had acute urinary retention (AUR) or a surgical intervention in the arm receiving the combination was 4.2% (67/1,610) and in the tamsulosin arm was 11.9% (191/1,611), i.e., the absolute risk reduction was 7.7% [7.1% - 8.3%]; the relative risk reduction (RRR) was 65.8% [54.7% - 74.1%].

A comparison between the combination-treated and dutasteride-treated groups treated was not part of the study design (power not sufficient given the hypotheses); therefore no test of this hypothesis was planned and no difference was expected.
## Secondary efficacy endpoints

Variation after 4 years of treatment:

### Table 2

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Concomitant administration</th>
<th>dutasteride</th>
<th>tamsulosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical progression* (%)</td>
<td>12.6</td>
<td>17.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IPSS (units)</td>
<td>16.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.4</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td>(score on inclusion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-6.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-5.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-3.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(variation compared with the score on inclusion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal urine flow rate (ml/sec)</td>
<td>10.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.6</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>(value on inclusion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.0</td>
<td>0.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(variation compared with the value on inclusion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>54.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>54.6</td>
<td>55.8</td>
</tr>
<tr>
<td></td>
<td>(value on inclusion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 27.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- 28.0</td>
<td>+ 4.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(%variation compared with the value on inclusion)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Quality of life:

- BPH Impact Index (BII) (units)  
  - 5.3<sup>b</sup>  
  - 2.2<sup>b</sup>  
  - 1.8<sup>b</sup>  
  - 1.2<sup>a</sup>

- IPSS question 8: quality of life in BPH (units)  
  - 3.6<sup>b</sup>  
  - 1.5<sup>b</sup>  
  - 1.3<sup>b</sup>  
  - 1.1<sup>a</sup>

*Clinical progression was defined as a composite endpoint including a ≥ 4 point decrease in IPSS, the occurrence of BPH-related AUR, incontinence, urinary infection and renal insufficiency

<sup>a</sup>Significance level of concomitant administration vs. tamsulosin (p<0.001) at 48 months

<sup>b</sup>Significance level of concomitant administration vs. dutasteride (p<0.001) at 48 months

---

Other data presented for information purposes: other studies that evaluated the benefit of combining an α-blocker with a 5-ARI

Until 2003, the clinical benefit of combining an α-blocker with a 5-ARI (finasteride) for the treatment of BPH symptoms had not been demonstrated in placebo-controlled studies lasting one year (Kirby RS et al, 2003, Lepor H et al, 1996<sup>8</sup>). The benefit of the combination was suggested by the results of the MTOPS<sup>9</sup> study.

The MTOPS study had suggested the benefit of combining an α-blocker and a 5-ARI. This study compared the efficacy and safety of treatment with finasteride 5 mg/day (n = 768), doxazosin 4-8 mg/day (n = 756), a finasteride + doxazosin combination at the same dosages as in monotherapy (n = 786) and a placebo (n = 737) in patients with moderate to severe BPH symptoms. This randomised, double-blind study with an average duration of 5 years had as its primary efficacy endpoint the time to onset of clinical BPH progression defined by a composite endpoint including: an increase of 4 points or more compared with the baseline value, an increase in the symptom score measured on a symptom scale (counting 35 points in total) validated by the American Urological Association (confirmed 2 to 4 weeks later), the

---

<sup>8</sup>These two studies were referenced for the calculation of the target population.

onset of acute urinary retention, the onset of BPH-related renal insufficiency (defined by a 50% increase in serum creatinine from the baseline value, reaching at least 1.5 mg/dl and confirmed after 4 weeks), the onset of a recurrent or serious urinary tract infection and the onset of urinary incontinence. Treatment with finasteride alone led to a 34% reduction versus placebo (p = 0.0018) in the risk of BPH progression (finasteride: 11.6%, placebo: 17.4%). Most (around 80%) of the events that contributed to BPH progression were related to an increase of 4 points or more in the symptom score. The reduction in the risk of BPH progression was also significant in the doxazosin group and with the combination (reduction of 39% and 67% respectively).

The incidence of BPH clinical progression with the combination (6.2%) was about 5% lower than with finasteride alone (11.6%; p < 0.001) or doxazosin alone (11.2%; p < 0.001).

The risk of acute urinary retention occurrence was significantly lower in the finasteride group than in the placebo group (0.8% versus 2.4%, p = 0.0114). The reduction in the risk of acute urinary retention occurrence was not statistically significant in the doxazosin group (1.7% versus 2.4%, p = 0.2963), whereas it was with the combination (0.5% versus 2.4%, p = 0.0013). Likewise, compared with placebo, finasteride significantly reduced the need for BPH-related surgery (2.0% versus 5.4%, p = 0.0004). The reduction in the risk of BPH-related surgery was not significant compared with placebo in the doxazosin group (5.4% versus 5.4%, p = 0.8686), whereas it was with the combination (1.8% versus 5.4%, p = 0.0001). Comparing the MTOPS and CombAT results is unreliable as the patient characteristics and the primary analysis endpoints are different.

3.2. Adverse effects

3.2.1. Data from clinical studies

- In monotherapy:

The most frequent adverse effects with dutasteride are impotence, reduced libido, ejaculation disorders, breast disorders (including breast swelling and/or tenderness) and allergic reactions. The SmPC points out that dutasteride can affect sperm (by reducing the number of spermatozoa, the volume of ejaculate and spermatozoa motility) in healthy men and reduced male fertility cannot be excluded. Spontaneous reports have revealed the possible occurrence of allergic reactions such as skin rashes, pruritis, urticaria, localised oedema and angioedema.

Dizziness is the most frequent adverse effect (≥1/100 and ≤1/10) with tamsulosin. As with other alpha blockers, treatment with tamsulosin can lead to low blood pressure and in rare cases can cause syncope. Intraoperative floppy iris syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in patients who had been treated with tamsulosin. This syndrome may lead to more frequent technical complications during cataract surgery. The SmPC therefore advises against initiating therapy with COMBODART when a cataract operation is scheduled.

- Breast cancer on 5-ARI:

In the three pivotal studies, three cases of breast cancer in men were reported: two cases in men receiving 0.5 mg/day of dutasteride and one case in a man who received a placebo. These three cases were reported during the same double-blind, placebo-controlled 2-year trial with an additional 2-year open-label follow-up. These two observations, mentioned in the SmPC (§ 5.1) since dutasteride was made available in France in 2003, have resulted in the monitoring of this potential risk (biannual review and specific follow-up questionnaire). Since then, two phase III clinical trials have been carried out with a 4-year follow-up period: the ARI40005/CombAT trial in which 3233 patients received dutasteride (monotherapy arm and combination arm) and the ARI40006/REDUCE trial in which 4105 subjects took dutasteride for 4 years. There was no breast cancer reported in the male subjects of these two trials. According to the pharmacovigilance data supplied by GSK (Table 3), the latest PSUR reports 15 cases of breast cancer reported or confirmed by health professionals (spontaneous reports) around the world in the post-marketing period. Of these cases, 8 were observed in the USA, 7 in Europe (no cases in France), 1 in Canada and 1 in Brazil. No cases have been
reported in the literature. The mean age observed in the cases was 72 ± 6 years (5 cases had missing data) and the average time to cancer onset from the start of treatment was relatively short, 225 ± 104 days, i.e., around 7 months (8 cases had missing data) with a median time to onset of 8.5 months. The 17 cases were reported or confirmed by health professionals.

Table 3: Cumulative number of cases of breast cancer in men compared with the estimated dutasteride exposure and calculated incidence

<table>
<thead>
<tr>
<th></th>
<th>May-07</th>
<th>May-08</th>
<th>Nov-09</th>
<th>May-10</th>
<th>Nov-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative number of breast cancer cases</td>
<td>6</td>
<td>10</td>
<td>13</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Estimated exposure to dutasteride (million patient-years)</td>
<td>1.9</td>
<td>2.9</td>
<td>4.4</td>
<td>5.2</td>
<td>6.6</td>
</tr>
<tr>
<td>Incidence (per 100,000 patient-years)</td>
<td>0.32</td>
<td>0.34</td>
<td>0.30</td>
<td>0.29</td>
<td>0.26</td>
</tr>
</tbody>
</table>

In the general population, the incidence of breast cancer in men of the same age as those exposed to the 5-ARIs is reportedly 4 to 9 per 100,000 person-years. Given the data provided by GSK (cf. Table 3), there is reportedly no increased risk of breast cancer with dutasteride treatment.

The European (EMA) and North American (FDA) regulatory agencies recently evaluated this risk for proprietary medicinal products containing dutasteride or finasteride. The current SmPCs for AVODART and COMBODART specify that “to date, the relationship between long-term use of dutasteride and breast cancer in men is not clearly established”.

Cases of breast cancer in men were also reported with finasteride (CHIBRO PROSCAR); the SmPC for CHIBRO PROSCAR now shows that “cases of breast cancer have been reported, during clinical studies and in the post-marketing period, in men treated with a 5 mg dose of finasteride”. Doctors will need inform their patients that they must promptly report any changes in their breast tissue such as lumps, pain, gynecomastia or nipple discharge.”

- Prostate cancer on 5-ARI:

The risk of prostate cancer has been monitored since 2008 as part of the risk management plan (RMP) as an event of interest. The risk of “prostate cancer and high-grade tumours” is a new item included in the SmPC.

In the CombAT study carried out over 4 years in BPH, the rate of cancer with a Gleason score of 8 to 10 was 0.5% (n = 8) for AVODART, 0.7% (n = 11) with tamsulosin and 0.3% (n = 5) with the combination. This study the protocol did not plan for a routine biopsy to be done to test for cancer.

One study (REDUCE) evaluated the efficacy of dutasteride 0.5 mg/day compared with placebo in reducing the risk of prostate cancer in high-risk patients: 8231 men aged 50 to 70 with a prior negative biopsy for prostate cancer and a baseline PSA value of 2.5 ng/ml to 10.0 ng/ml for the men aged 50 to 60 and 3 ng/ml to 10.0 ng/ml for the men over the age of 60. Analyses of the biopsies aimed to determine the presence or absence of prostate cancer and its grade according to the Gleason histological score (low grade: ≤ 6 or high grade with two different definitions for the high grade: a score of 7-10 or 8-10).

After 4 years of treatment, the biopsies of 6706 subjects were available. A prostate cancer diagnosis was made in 1517 of these patients. The majority of prostate cancers detected by biopsy in the two treatment groups were low grade (Gleason 5 and 6, 70%).

A higher incidence of higher-grade prostate cancers (Gleason score of 8 to 10) was observed in the dutasteride group (n = 29, 0.09%) compared with the placebo group (n = 19, 0.06%) (p = 0.15, NS difference). After 1 and 2 years of treatment, the number of subjects with a Gleason score of 8 to 10 was similar in the AVODART group (n = 17, 0.5%) and the
placebo group (n = 18, 0.5%). In contrast, after 3 and 4 years of treatment, the number of cancers with a Gleason score of 8 to 10 was higher in the AVODART group (n = 12, 0.5%) than in the placebo group (n = 1, <0.1%), p = 0.0035. The percentage of patients diagnosed with a Gleason score of 8 to 10 did not vary during the study (years 1-2 and years 3-4) in the AVODART group (0.5% in each period). In the placebo group, this percentage was 0.5% after 1 and 2 years of treatment and <0.1% after 3 and 4 years (NS difference).

Cases of high-grade tumours were also observed on finasteride (CHIBRO PROSCAR). On 6 September 2011, the FDA informed health professionals and patients of a possible increased risk of high-grade prostate cancer with 5-ARI medicines. It was based on the results of the PCPT and REDUCE studies. The PCPT study evaluated the effect of finasteride (5 mg/day) versus placebo for 7 years on the reduction of prostate cancer risk in men aged 50 or over. Both these studies demonstrated an overall reduction in prostate cancer diagnoses, but this reduction was due to a lower incidence of low-risk cancers ("lower risk forms"). However, in both studies, there was an increased incidence of high-grade prostate cancers in patients receiving finasteride and dutasteride (cf. CHIBRO-PROSCAR registration renewal notice of 5 September 2012).

During concomitant administration, according to the data from the CombAT trial, there were more adverse effects during the 1st year of treatment in the combination arm (22%) than in the dutasteride (15%) and tamsulosin (13%) arms. This higher incidence in the combination arm can be explained by an increased incidence of impotence and libido disorders, and in particular ejaculation disorders (Table 4). There was no difference in adverse effect incidence between the three arms during the 2nd year.

---

Table 4: Incidence of adverse effects during the first two years in CombAT

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse effect</th>
<th>Incidence during the 1\textsuperscript{st} year of treatment</th>
<th>Incidence during the 2\textsuperscript{nd} year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dutasteride + tamsulosin (n=1610)</td>
<td>dutasteride (n=1623)</td>
<td>tamsulosin (n=1611)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders, psychiatric disorders and investigations</td>
<td>Impotence</td>
<td>6.5%</td>
<td>4.9%</td>
</tr>
<tr>
<td></td>
<td>Change in libido (reduction)</td>
<td>5.2%</td>
<td>3.8%</td>
</tr>
<tr>
<td></td>
<td>Ejaculation disorders</td>
<td>8.9%</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Breast disorders (swelling and/or breast tenderness)</td>
<td>2.0%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>1.4%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

- Cardiac failure:

After the 4-year follow-up in the CombAT trial, the incidence of the composite term “cardiac failure” was 0.9% (14/1610) in subjects receiving the combination, 0.2% (4/1623) in those receiving dutasteride monotherapy and 0.6% (10/1611) in those receiving tamsulosin.

In the REDUCE trial (8231 men aged 50 to 75 with no cancer histology on a prostate biopsy at inclusion and an initial PSA value of 2.5 ng/ml to 10.0 ng/ml in the men aged 50 to 60, or of 3 ng/ml to 10.0 ng/ml in the men over the age of 60), there was a higher incidence of cardiac failure\textsuperscript{11} in subjects taking 0.5 mg of AVODART per day (30/4105, 0.7%) than in subjects taking the placebo (16/4126, 0.4%). A post-hoc analysis of this study showed a higher incidence of cardiac failure in subjects taking AVODART with an alpha blocker (12/1152, 1.0%) than in subjects taking AVODART without an alpha blocker (18/2953, 0.6%), or taking an alpha blocker alone (1/1399, <0.1%) or taking neither 5-ARI nor an alpha blocker (15/2727, 0.6%).

The SmPC specifies that there no causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (Table 5). According to the FDA analysis, the link has not yet been established as the majority of cases in these two studies had associated co-morbidities and a risk of cardiac failure.

- During the Marketing Authorisation procedure, a comparison was made of the safety data from the CombAT study and the data from three clinical studies comparing dutasteride monotherapy (n = 2167) with a placebo (n = 2158). The adverse effects after 1 and 2 years of treatment were similar in type and frequency to those observed in the dutasteride monotherapy arm of the CombAT study. No change in the adverse effect profile was observed during the subsequent 2 years of the open-label extension phase of these studies.

\textsuperscript{11} The “Cardiac failure” endpoint was composed of the following events: “congestive cardiac failure, cardiac failure, left ventricular failure, acute cardiac failure, cardiogenic shock, acute left ventricular failure, right ventricular failure, acute right ventricular failure, ventricular failure, cardiopulmonary failure, congestive cardiomyopathy.”

12/16
3.3. Conclusion

No studies have evaluated the clinical benefit of a fixed-dose combination of dutasteride and tamsulosin in the treatment of benign prostatic hyperplasia.

The clinical benefit in taking dutasteride and tamsulosin concomitantly compared with dutasteride- or tamsulosin-based monotherapies was evaluated in a phase IIIb study (ARI40005, the so-called “CombAT trial”) of 4,844 benign prostatic hyperplasia (BPH) patients considered at risk of progression. The objective was to establish the superiority of taking dutasteride and tamsulosin concomitantly versus taking each as monotherapy in improving BPH symptoms after 2 years of treatment and in reducing complications after 4 years of treatment.

After 2 years of treatment, the adjusted difference in the mean IPSS variation was -1.3 points [-1.69; -0.86], p<0.001 between the combination and dutasteride arms and -1.8 points [-2.23; -1.40], p<0.001 between the combination and tamsulosin arms. The extent of this difference is modest, which raises questions about its clinical relevance.

After 4 years of treatment, the time to onset of an event (AUR episode or BPH-related surgery) was longer (p<0.001) in the arm receiving the combination than in the arm receiving tamsulosin. The percentage of patients who had acute urinary retention (AUR) or a surgical intervention in the arm receiving the combination was 4.2% (67/1,610) and in the tamsulosin arm was 11.9% (191/1,611), i.e., the absolute risk reduction was 7.7% [7.1% - 8.3%]; the relative risk reduction (RRR) was 65.8% [54.7% - 74.1%].

There was no difference between the combination and dutasteride arms on the primary endpoint after 4 years of treatment. Tamsulosin did not demonstrate any effect on prevention of these complications; the addition of this alpha blocker does not increase the already established efficacy of dutasteride.

The efficacy results in favour of the combination were obtained, but at a cost of increased reproductive system disorders (impotence, libido disorders), and in particular ejaculation disorders during the 1st year of treatment.

The risk of breast cancer with the 5-ARIs (dutasteride, finasteride) continues to be monitored by the regulatory authorities. To date, it has not been established.

According to the SmPC, “in two 4-year clinical studies, the incidence of ‘cardiac failure’ (a composite term of reported events, basically cardiac failure and congestive cardiac failure) was higher in subjects taking the AVODART combination and an alpha blocker, principally tamsulosin, compared with subjects not taking the combination”. Nevertheless, the SmPC specifies that “in both studies, the incidence of cardiac failure was low (<1%) and variable between the studies.” According to the FDA analysis, the link remains unestablished, especially since the majority of subjects with cardiac failure in these two studies had associated co-morbidities, with an increased risk of cardiac failure.

In men with an increased risk of prostate cancer, a higher incidence of high-grade prostate cancers (with a Gleason score of 8 to 10) was observed in men treated with dutasteride (AVODART) compared with those taking a placebo in a clinical study (REDUCE trial) after 3 to 4 years of treatment. The causal relationship between dutasteride and high-grade prostate cancer has not been clearly established. Men treated with dutasteride must have their prostate-cancer risk regularly assessed.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Uncomplicated Benign Prostatic Hyperplasia (BPH) is a disorder with symptoms that can affect a patient’s quality of life. BPH reportedly does not increase the risk of prostate cancer.

COMBODART is intended to treat the symptoms of BPH and aims to reduce the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe BPH symptoms.

Public health benefit

Benign prostatic hyperplasia is a common, most often benign disease. However, it which can impair a patient’s quality of life (e.g., by causing urinary frequency and/or dysuria). In the medium and long term, the severity of this disease is related to the occurrence of acute urinary retention, which can lead to surgical intervention. In terms of DALYs, the burden of this disease may be considered moderate.

Management of this disease does not represent a public health priority.

Given the available data, the impact of the combination on the symptoms and on morbidity (acute urine retention and surgical intervention for BPH) is limited compared with the impact of each medicine (dutasteride and tamsulosin) as monotherapy. Furthermore, there is no data comparing the COMBODART fixed combination and the freely combined medications.

Transferability of the data to current medical practice seems to be acceptable. However, the patients included in the trial all presented a risk of disease progression (prostate volume ≥ 30 ml and total serum PSA level of 1.5 to 10 ng/ml), which could differ from standard practice. In addition, there is a risk of misuse by using the fixed combination straightaway when monotherapy alone could suffice.

COMBODART has no impact on the health care system.

In summary, no public health benefit is expected for the COMBODART proprietary medicinal product in benign prostatic hyperplasia.

There are alternatives to taking COMBODART, including taking the two active ingredients of this proprietary medicinal product separately or taking another alpha blocker and/or another 5-ARI.

The efficacy/adverse effects ratio of the tamsulosin + dutasteride combination is low given the low level of the effect and the and the risk for adverse effects, particularly during the first 6 months of treatment. In addition, an increased risk of breast cancer or high-grade prostate cancer on dutasteride cannot be excluded.

COMBODART is a second line medicine, prescribed as an alternative to taking the two medicines separately.

Consequently, the Committee considers that the actual benefit of COMBODART is:
- low when it is prescribed as a replacement for separate doses of tamsulosin and dutasteride, provided that this combination has been well tolerated during at least 6 months of treatment
- insufficient as a first-line treatment or when prescribed following monotherapy with dutasteride or tamsulosin.

The Committee notes that fixed-dose combinations of this type expose patients to a risk of prescription confusion and of drug interactions due to a frequent lack of knowledge about the active ingredients combined in the proprietary medicinal product.
4.2. Improvement in actual benefit (IAB)

COMBODART provides no improvement in actual benefit (IAB V) in the management of benign prostatic hyperplasia.

4.3. Therapeutic use of COMBODART

According to the guidelines of of the Agence nationale d’accréditation et d’évaluation en santé (ANAES, or the French Agency for Accreditation and Evaluation of Health Care), men with uncomplicated benign prostatic hyperplasia (BPH) and moderate symptoms that they deem acceptable (provided there is no impact on the bladder or the upper urinary tract) should not be treated.

Initiation of medical treatment basically depends on the discomfort caused by the symptoms and the impact on the patient’s quality of life. Substantial prostatic volume does not, on its own, constitute a criterion for initiating treatment.

When drug treatment proves necessary, alpha blockers or plant extracts can be used as first-line therapy. Medicines in the 5-ARI class (AVODART, CHIBRO-PROSCAR) have demonstrated clinical efficacy in BPH treatment. According to several recommendations, they can be prescribed for patients at high risk of disease progression (such as elderly patients) who have an increased prostate volume (more than 30 g) and a high PSA level (higher than 1.4 ng/ml). Nevertheless, the fact that these medicines may expose patients to an increased risk for breast cancer and high-grade prostate cancer cannot be ignored. These medicines are second-line treatments in the event of treatment failure with herbal medicines and/or alpha blockers.

The additional efficacy of the tamsulosin + dutasteride combination was low compared with tamsulosin alone and was obtained at a price of an increased risk for discontinuing treatment due to adverse effects, particularly during the first 6 months of treatment (CombAT study). Replacing the combination of the two active ingredients taken separately (dutasteride + tamsulosin) with the fixed-dose combination (COMBODART) should only be considered in patients for whom a clinical benefit is observed with acceptable safety after at least 6 months of this treatment.

4.4. Target population

The COMBODART target population is represented by adult males with moderate to severe BPH symptoms at risk of disease progression (prostate volume of more than 30 ml) and for whom at least 6 months of treatment with a alpha blocker + 5-alpha reductase inhibitor dual therapy was associated with clinical benefit and acceptable safety.

In a French study conducted with 2011 men aged 50 to 80 years in 1992, the prevalence of moderate to severe BPH symptoms (IPSS score > 7) was estimated at 14.2%. In a Dutch study, 75.5% (1341/1776) of patients aged 50 to 80 years suffering from lower urinary tract symptoms had a prostate volume greater than 30 ml. Based on this data, the number of men

---

with moderate to severe BPH symptoms at risk of disease progression is reportedly 1 million at most.
The population likely to come within the scope of treatment with the combination of an alpha blocker and a 5-alpha reductase inhibitor is unknown.
For information, according to the EGB data\textsuperscript{19} extrapolated to the entire French population in 2011, the number of people who had at least one dispensation of an alpha blocker and a 5-alpha reductase inhibitor was estimated at 324,038 (95% CI, 312,399 to 335,677). The number of people who had at least one dispensation of dutasteride and tamsulosin was estimated at 54,025 (95% CI, 49,462 to 58,787).

In summary, the target population for COMBODART is difficult to quantify in the absence of data on the number of patients treated with well-tolerated dual therapy for at least 6 months. It is reportedly 54,000 patients at most.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage mentioned in the Marketing Authorisation.

Consequently, the Committee considers that the actual benefit of COMBODART is:
- low when it is prescribed as a replacement for separate doses of tamsulosin and dutasteride, provided that this combination has been well tolerated during at least 6 months of treatment
- insufficient as a first-line treatment or when prescribed following monotherapy with dutasteride or tamsulosin.

Reimbursement rate: 15%.

Packaging: Appropriate for the prescription conditions.

\textsuperscript{19} The EGB (Echantillon Généraliste des Bénéficiaires) is a representative sample (1/97\textsuperscript{th}) of all French people covered by National Insurance. It contains anonymous information about the demographic characteristics of people, paid benefits and chronic (long-term) conditions since 2003. The extrapolation of EGB data to the French population was done by calculating an extrapolation coefficient. This extrapolation coefficient was obtained dividing the number of beneficiaries in the EGB on 1 January 2011 (n = 594,370) by the French population on 1 January 2011 (n = 65,001,181). The extrapolation coefficient obtained was 1/109.36.