

An addendum from the November 2024 PBAC Meeting has been added to the end of this document.

5.04 DROSPIRENONE WITH ETHINYLESTRADIOL,

Pack containing 24 tablets 3 mg drospirenone with 20 micrograms ethinylestradiol (as betadex clathrate) and 4 inert tablets,

Pack containing 21 tablets 3 mg drospirenone with 30 micrograms ethinylestradiol (as betadex clathrate) and 7 inert tablets,

Yaz[®], Yasmin[®],

Bayer Australia Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested an Unrestricted benefit listing for drospirenone with ethinylestradiol in the following forms:

- Pack containing 24 tablets 3 mg drospirenone with 20 micrograms ethinylestradiol (as betadex clathrate) and 4 inert tablets (Yaz[®])
- Pack containing 21 tablets 3 mg drospirenone with 30 micrograms ethinylestradiol (as betadex clathrate) and 7 inert tablets (Yasmin[®]).

1.2 Listing was requested as an Unrestricted benefit to align with other combined oral contraceptive (COC) medications currently listed on the Pharmaceutical Benefits Scheme (PBS).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Individuals requiring oral contraception (Unrestricted benefit)
Intervention	Yaz: 1 tablet daily on a continuous basis (contains 24 active tablets and 4 inert tablets) Yasmin: 1 tablet daily on a continuous basis (contains 21 active tablets and 7 inert tablets)
Comparator	The submission did not nominate a comparator Any COCs currently PBS-listed could be considered alternative comparators
Outcomes	Contraception
Clinical claim	Yaz has comparable contraceptive efficacy and tolerability to the COC Marvelon [®] (desogestrel 150 micrograms and ethinylestradiol 30 micrograms (21 tablets) and 7 inert tablets), and comparable bleeding and cycle control. Yasmin has comparable contraceptive efficacy compared to the COC Marvelon, and has comparable bleeding and cycle control. Yasmin's tolerability is comparable to other COCs. Yasmin has demonstrated improvements in body weight compared to Marvelon, and improvements in wellbeing and menstrual distress.

Source: pp16,21,58-82 of the submission.

COC=combined oral contraceptive

2 Background

- 2.1 The submission referred to the *National Women’s Health Strategy 2020-2030* which aims to support ongoing improvement in the health and wellbeing of Australian women. One of the priorities is to increase access to sexual and reproductive health care information, diagnosis, treatment and services.
- 2.2 An action for this priority is to remove barriers to support equitable access to timely, appropriate and affordable care for all women. This includes working towards universal access to sexual and reproductive health information, treatment and services that offer options to women to empower choice and control in decision-making about their bodies, including contraception, as well as improving access to and uptake of appropriate contraceptive measures.
- 2.3 The submission referred to The Senate Community Affairs Reference Committee (2023) ‘Ending the postcode lottery: Addressing barriers to sexual, maternity and reproductive healthcare in Australia’. The report from the inquiry noted that ‘enabling universal access to reproductive healthcare has the profound capacity to improve community health and well-being, develop a culture of inclusion and safety, and enhance workforce participation.’
- 2.4 The inquiry identified barriers individuals face when attempting to access effective contraception, including contraceptives not available on the PBS. High financial costs of accessing contraceptives were identified as a key barrier to universal access.
- 2.5 The inquiry stated that the PBS subsidises oral contraceptives that contain ethinylestradiol combined with either levonorgestrel or norethisterone, and progestogen only contraceptives containing levonorgestrel or norethisterone. The inquiry noted that oral contraceptives containing newer oestrogens and progestogens are available, however are not listed on the PBS. The Committee ‘considers that improved consumer choice will result in higher acceptability, satisfaction, and continuation rates of effective contraception within the community. Given this, the committee recommends that the Government works with industry to expand and improve the PBS to include newer forms of the OCP (oral contraceptive pill).....’.

Registration status

- 2.6 Yasmin was Therapeutic Goods Administration (TGA) registered in 2002 for use as an oral contraceptive.
- 2.7 Yaz was TGA registered on 4 August 2014 for use as:
 - an oral contraceptive
 - treatment of moderate acne vulgaris in women who seek oral contraception
 - treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraceptives as their method of birth control (the efficacy of Yaz for PMDD was not assessed beyond three cycles).

Yaz has not been evaluated for the treatment of premenstrual syndrome.

- 2.8 The recommended dose is one tablet taken daily at about the same time each day continuously. One pack lasts 28 days, and another pack is started the day after the last tablet from the previous pack. Withdrawal bleeding usually begins 2-3 days after starting the placebo tablets, and may not have finished by the time the new pack is started.

Previous PBAC consideration

- 2.9 Yaz and Yasmin have not been considered by the PBAC previously.
- 2.10 The submission noted that both Yaz and Yasmin have been TGA registered for approximately 10 years or more and have been available to Australian patients on the private market.

Current PBS listings for combined oral contraceptives

- 2.11 The following combined oral contraceptives (COCs) are currently listed on the PBS as Unrestricted benefit listings:
- levonorgestrel 100 microgram + ethinylestradiol 20 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Femme-Tab[®] ED 20/100)
 - levonorgestrel 125 microgram + ethinylestradiol 50 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Microgynon[®] 50 ED)
 - levonorgestrel 150 microgram + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Eleanor 150/30 ED, Evelyn 150/30 ED, Femme-Tab 30/150 ED, Lenest[®] 30 ED, Micronelle[®] 30 ED, Leven[®] ED)
 - levonorgestrel 50 microgram + ethinylestradiol 30 microgram tablet [6] (& levonorgestrel 75 microgram + ethinylestradiol 40 microgram tablet [5] (& levonorgestrel 125 microgram + ethinylestradiol 30 microgram tablet [10] (& inert substance tablet [7], 4 x 28 (Logynon[®] ED, Trifeme[®] 28, Triquilar[®] ED)
 - norethisterone 1 mg + ethinylestradiol 35 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Norimin-1 28 Day)
 - norethisterone 500 microgram + ethinylestradiol 35 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Norimin 28 Day).
- 2.12 At its November 2012 meeting, the PBAC recommended listing levonorgestrel with ethinylestradiol, tablet, 100 micrograms-20 micrograms, Femme-Tab ED, as an unrestricted benefit listing on a cost-minimisation basis with levonorgestrel 150 micrograms with ethinylestradiol 30 micrograms combination tablets.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The submission requested the following new listing. Suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DROSPIRENONE WITH ETHINYLESTRADIOL					
drospirenone 3 mg + ethinylestradiol 20 microgram tablet [24] (& inert substance tablet [4], 28	NEW	1	1	11	Yaz
drospirenone 3 mg + ethinylestradiol 20 microgram tablet [24] (& inert substance tablet [4], 3 x 28	NEW	1	3	3	Yaz
drospirenone 3 mg + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 28	NEW	1	1	11	Yasmin
drospirenone 3 mg + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 3 x 28	NEW	1	3	3	Yasmin
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners				
	Restriction type: <input checked="" type="checkbox"/> Unrestricted benefit				
	Indication: Contraception				
	Treatment Phase: Initial and continuing treatment				

3.2 The submission requested Unrestricted benefit listings for Yaz and Yasmin. It noted that the indication would be for contraception, however Yaz is also TGA registered for the treatment of moderate acne vulgaris and symptoms of PMDD in women using oral contraception. As the requested listings are for Unrestricted benefit listings, access to these medicines through the PBS would not be dependent on use for these indications.

3.3 The requested listing included the maximum number of repeats to allow for up to 12 months of treatment, consistent with other PBS-listed COCs.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

Mechanism of action

4.1 COCs have a progestogen and estrogen, and exert their contraceptive effects by inhibiting ovulation and thickening cervical mucus to act as a barrier to sperm.¹

¹ The Royal Australian and New Zealand College of Obstetricians and Gynaecologists., (2019), 'Combined hormonal contraceptives', <https://ranzcof.edu.au/wp-content/uploads/2022/05/Combined-hormonal-contraceptives.pdf>

- 4.2 In addition to contraception, COCs also have other effects that may be viewed as beneficial, such as regulation of menstrual cycle, reduction of pain associated with menstruation, reduction of heavy menstrual bleeding, reduction of symptoms of endometriosis, management of symptoms of polycystic ovarian syndrome, and management of pre-menstrual syndrome and PMDD in some women (RANZCOG Combined hormonal contraceptives).
- 4.3 Drospirenone has anti-mineralocorticoid activity, which opposes estrogen-related sodium retention and has anti-androgenic activity. Drospirenone does not counteract the ethinylestradiol-related sex hormone binding globulin increase that is useful for binding and inactivating endogenous androgens. Drospirenone also has no androgenic, estrogenic, glucocorticoid and anti-glucocorticoid activity. These features give drospirenone a biochemical and pharmacological profile similar to natural progesterone (Yasmin Product Information).

Population

- 4.4 The submission stated that unintended pregnancies remain a public health concern in Australia, and has health, social, psychological and economic consequences. Unintended pregnancies can lead to interrupted schooling, affects an individual's ability to gain work experience and establish careers, and is associated with depression and anxiety.² Babies born from unintended pregnancies are more likely to have poorer antenatal care and a higher risk of infant mortality.³
- 4.5 The submission stated that 80% of Australian women aged 16-49 years use contraception,⁴ however 1 in 4 women aged 18-51 years experience an unintended pregnancy, and 1 in 6 have an abortion in their lifetime.^{5,6}
- 4.6 Contraceptive efficacy is typically reported by the Pearl Index. The Pearl Index is defined by the number of contraceptive failures per 100 women-years of exposure. A highly effective contraceptive has a Pearl Index <0.5. The Food and Drug Administration (FDA) guidance (2019)⁷ for establishing effectiveness for hormonal

² Sonfield A, Hasstedt K, et al, (2013), 'The Social and Economic Benefits of Women's Ability to Determine Whether and When to Have Children', www.guttmacher.org/pubs/social-economic-benefits.pdf

³ Gipson JD, Koenig MA, et al, (2008), 'The effects of unintended pregnancy on infant, child, and parental health: a review of the literature', *Studies in Family Planning*, 39(1):pp.18-38.

⁴ Richters J, Fitzadam S, et al, (2016), 'Contraceptive practices among women: the second Australian study of health and relationships', *Contraception*, 94(5):pp.548-555.

⁵ Rowe H, Holton S, et al, (2016), 'Prevalence and distribution of unintended pregnancy: the Understanding Fertility Management in Australia National Survey', *Australian and New Zealand Journal of Public Health*, 40(2):pp.104-109.

⁶ Rowe H, Holton S, et al, (2017), 'Abortion: findings from women and men participating in the Understanding Fertility Management in contemporary Australia national survey', *Sexual Health*, 14(6):pp.566-573.

⁷ Food and Drug Administration (FDA), (2019), 'Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy Guidance for Industry - Draft Guidance', Center for Drug Evaluation

contraceptives recommended that calculation of the Pearl Index should only include cycles during which:

- there was vaginal intercourse, and
- no backup or emergency contraception was used.

It was noted that COCs are very effective at preventing pregnancy, typically having an upper bound of the 95% confidence interval (CI) below 5 in trials.

4.7 The effectiveness of a contraceptive method is user dependent. The effectiveness for typical use is defined by pregnancy rates during actual use, including inconsistent or incorrect use, and perfect use is defined as following the directions for use.

4.8 Table 2 presents the Pearl Index and effectiveness of typical and perfect use of selected contraceptive methods.

Table 2: Contraceptive efficacy of selected contraception methods

Method	Pearl Index ^a	Effectiveness – typical use (%)	Efficacy – perfect use (%)
Combined oral contraceptives	0.01-2.36	93	99.5
Injectable hormones	0.03-0.9	96 [^]	99.8 [^]
Levonorgestrel intrauterine system	0.1	99.7-99.9	99.7-99.9
Female Sterilisation	0.1	99.5	99.5
Mini-pill (<i>progestin only pill</i>)	0.4-4.3	93	99.5
Male condom	7-14	88	98
Diaphragm + spermicide	2-25	88 ^b	94 ^b
Diaphragm	6-29	82	86
Coitus interruptus	10-40	80	96
Implant*	0.0-0.018	99.95	99.95
No contraception	>80	15	15

Source: Table 1, p19 of the submission, Trussell 2011, Therapeutic Guidelines Australia.

* TGA approved PI for Implanon.

[^] effectiveness of medroxyprogesterone depot

^a Number of unplanned pregnancies per 100 woman-years of use

^b Based on Trussell 2011 reported % of women experiencing unintended pregnancy within first year of use for diaphragm with spermicide of 12% for typical use and 6% for perfect use.

4.9 The submission stated that Yaz and Yasmin have an established place in therapy for their registered indication of contraception according to Australian clinical guidelines, such as the electronic Therapeutic Guidelines.

4.10 While comparative effectiveness studies are limited, clinical guidelines generally do not recommend any one contraceptive pill formulation over another. The estimated effectiveness and efficacy of COCs are also user-dependent; its failure rate differs between ‘perfect use’ in women who take it consistently and correctly and ‘typical use’ when the pill is used inconsistently or incorrectly (Stewart and Black 2015⁸). A

and Research, US, www.fda.gov/regulatory-information/search-fda-guidance-documents/establishing-effectiveness-and-safety-hormonal-drug-products-intended-prevent-pregnancy-guidance

⁸ Stewart M, Black K, (2015), ‘Choosing a combined oral contraceptive pill’, *Aust Prescr*, 38(1):pp.6-11.

review (Teal and Edelman 2021⁹) of the efficacy and safety and choice of reversible contraceptives noted that in practice, clinicians typically start COC with the lowest ethinylestradiol dose to minimise risks (e.g. venous thromboembolism (VTE)). Further, despite differences in molecular structures of progestins, there is no evidence demonstrating that a particular progestin is superior to others in terms of contraceptive efficacy.

- 4.11 The Therapeutic Guidelines state that contraceptive choice is influenced by multiple factors, including contraindications and precautions, adverse effect profile, drug interaction potential, and non-contraceptive benefits (e.g. improvement in acne, dysmenorrhoea and heavy menstrual bleeding with some hormonal contraceptives).
- 4.12 The Therapeutic Guidelines recommend COCs containing levonorgestrel first-line for combined hormonal contraception. It suggests that using a COC containing drospirenone could be considered if the following adverse effects present with using COC:
- Breast tenderness;
 - Bloating and fluid retention (mild diuretic effect);
 - Mood changes if symptoms are exacerbated premenstrually.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission did not nominate a comparator, and stated that it was presenting a non-comparative approach.
- 5.2 The Pre-Sub-Committee Response (PSCR) claimed that the original trial data provided for TGA registration of Yaz and Yasmin were non-comparative studies, and since this time there have been no further studies comparing Yaz or Yasmin to other COCs. The PSCR claimed that comparative evaluation was therefore difficult and unreliable. The ESC noted the applicant's claims conflict with the evaluation, which noted the data provided for TGA registration of Yaz and Yasmin included comparative evidence with COCs containing ethinylestradiol with the progestogens desogestrel or levonorgestrel (see Clinical trials).
- 5.3 The PSCR stated that Yaz, if recommended for listing, would be the only COC available in a 24/4 (active/placebo tablets) formulation, and claimed that this formulation allows for better cycle control compared to other COCs. No evidence was provided to support this assertion.

⁹ Teal S, Edelman A, (2021), 'Contraception Selection, Effectiveness, and Adverse Effects: A Review', JAMA 326(24):pp.2507-2518.

5.4 For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice (Table 3):

Table 3: PBS-listed alternative therapies

Item	Brand name	TGA registered indications
COCs		
levonorgestrel 100 microgram + ethinylestradiol 20 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Femme-Tab ED 20/100	Oral contraception
levonorgestrel 125 microgram + ethinylestradiol 50 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Microgynon 50 ED	Oral contraception
levonorgestrel 150 microgram + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Eleanor 150/30 ED Evelyn 150/30 ED Femme-Tab 30/150 ED Lenest 30 ED Micronelle 30 ED Levlen ED	Oral contraception
levonorgestrel 50 microgram + ethinylestradiol 30 microgram tablet [6] (& levonorgestrel 75 microgram + ethinylestradiol 40 microgram tablet [5] (& levonorgestrel 125 microgram + ethinylestradiol 30 microgram tablet [10] (& inert substance tablet [7], 4 x 28	Logynon ED Trifeme 28 Triquilar ED	Oral contraception Prevention of pregnancy (Trifeme 28)
norethisterone 1 mg + ethinylestradiol 35 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Norimin-1 28 Day	Contraception
norethisterone 500 microgram + ethinylestradiol 35 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Norimin 28 Day	Contraception
Progestogen-only oral contraceptives		
levonorgestrel 30 microgram tablet	Microlut® 28	Oral contraception
norethisterone 350 microgram tablet	Noriday 28 Day	Oral contraceptive for women who will not, or cannot tolerate other oral contraceptives or intrauterine devices
Other		
etonogestrel 68 mg implant	Implanon® NXT	Contraception
medroxyprogesterone acetate 150 mg/mL injection	Depo-Ralovera® Depo-Provera®	<ul style="list-style-type: none"> • Carcinoma: palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma • Endometriosis: for use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful • Contraception (ovulation suppression): for long-term prevention of pregnancy in women when administered at 3-month intervals
levonorgestrel 19.5 mg intrauterine drug delivery system*	Kyleena®	Contraception for up to 5 years

Item	Brand name	TGA registered indications
levonorgestrel 52 mg intrauterine drug delivery system**	Mirena®	<ul style="list-style-type: none"> • Contraception • Treatment of idiopathic menorrhagia • Prevention of endometrial hyperplasia during estrogen replacement therapy

Source: PBS website (www.pbs.gov.au), Product Information

COCs = combined oral contraceptives, TGA = Therapeutic Goods Administration

*Restricted benefit for contraception

**Restricted benefits for contraception and idiopathic menorrhagia where oral treatments are ineffective or contraindicated

- 5.5 Some of these alternative therapies may be less costly than Yaz and Yasmin.
- 5.6 A further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

For more detail on PBAC’s view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician noted that all COCs are effective for contraception, and are commonly used for both contraceptive and non-contraceptive effects. The clinician stated that as the adverse effect profiles can vary between COCs it is important in clinical practice to have a range of COC options available to support patient choice and long term patient care, and provide options if patients experience adverse effects with one COC. If Yaz and Yasmin are listed on the PBS this would therefore provide alternative COC options for patients, where the cost can be prohibitive for patients currently. In addition, drospirenone is a newer, fourth generation progestogen, and there are currently no COCs with newer progestogens listed on the PBS. The clinician noted potential additional benefits with the use of Yaz and Yasmin, such as management of PMDD, providing another COC option with a lower dose estrogen, and having a shorter pill-free interval (less inactive tablets) with Yaz.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits with the use of Yaz and Yasmin outside of its contraceptive effects, including reduced menstrual pain and improvements in acne and managing PMDD. Comments stated that it was important in clinical practice to have a range of contraceptive options on the PBS to support women in accessing the contraceptive most appropriate for them. Comments also noted that the current cost of Yaz and Yasmin in the private market can be prohibitive

for patients, and can lead to reduced adherence and unintended pregnancy.

- 6.3 The National Aboriginal Community Controlled Health Organisation (NACCHO) stated that not having Yaz and Yasmin listed on the PBS can be a significant barrier to accessing these medicines for patients living in remote areas and obtaining medicines through the Remote Area Aboriginal Health Service S100 scheme. Having Yaz and Yasmin available on the PBS would therefore support improved access to these medicines for Aboriginal and Torres Strait Islander patients living in remote areas.

Clinical trials

- 6.4 For Yaz, the resubmission was based on two randomised open-label studies comparing Yaz to the COC Mercilon (desogestrel 150 micrograms with ethinylestradiol 20 micrograms) (A29551 and A09151) and two open-label non-comparative studies (A12007 and A30713) in women aged 18-36 years.
- 6.5 The submission also identified a pooled analysis of Yaz on contraceptive efficacy (Anttila 2011) across the four included open label studies (A29551, A09151, A12007 and A30713). The pooled analysis of Yaz on cycle control and bleeding pattern (Anttila 2011b) was not presented given it included a study with Yaz 21/7 regimen, which was inconsistent to the submission's requested dosing of Yaz 24/4 regimen.
- 6.6 For Yasmin, the clinical data was based on two head-to-head randomised trials (ME92052, ME93044) comparing Yasmin to the COC Marvelon (desogestrel 150 micrograms with ethinylestradiol 30 micrograms) and one open-label non-comparative study (96049B) in women aged 18-35 years. The submission included additional evidence from two studies of Yasmin (303121, Borenstein 2003) on quality of life and premenstrual symptoms and one study of Yasmin extended treatment regimen (i.e. without tablet-free intervals) (305511). The submission described ME92052, ME93044 and 96049B as the pivotal/primary trials, given they were included in the TGA registration of Yasmin. The TGA Clinical Evaluation Report (CER) for Yasmin noted a randomised, open-label trial of Yasmin versus Microgynon (levonorgestrel 125 micrograms/ethinylestradiol 30 micrograms) (study 90031), which was not identified in the submission. The TGA CER concluded that Yasmin was as effective as Marvelon and Microgynon in preventing pregnancy and cycle control as well as anti-androgenic and anti-mineralocorticoid action (body weight changes). Microgynon 50-ED (levonorgestrel 125 microgram/ethinylestradiol 50 microgram) is another COC currently available on the PBS, however no studies were identified comparing Yaz or Yasmin to this higher dose COC.
- 6.7 The evaluation identified additional trials of Yaz and Yasmin, which were potentially relevant. For Yaz, Marr 2015¹⁰ investigated the efficacy and safety of Yaz in Chinese

¹⁰ Marr J, Huang Z, et al., (2015), 'Efficacy and safety of an oral contraceptive containing ethinylestradiol 20 µg/drospirenone 3 mg (24/4 regimen) in three indications in the People's Republic of China: a comparison with international studies', *Open Access J Contracept* 6:95-104.

women over 13 cycles, and found that the efficacy, safety and tolerability were consistent with international studies included in the submission (A12007 and A30713). For Yasmin, Mansour 2011¹¹ compared Yasmin vs Zoely® (norgestrel acetate 2.5 mg with estradiol 1.5 mg) for contraceptive efficacy and cycle control over 13 cycles and Guang-Sheng 2010¹² compared Yasmin vs Marvelon for 13 cycles in Chinese women. The results showed that Yasmin was similar to Zoely and Marvelon in terms of efficacy and safety, with the exception of increased weight ($p < 0.001$) and premenstrual symptoms in the Marvelon group, consistent with the studies included in the submission (ME92052, ME93044).

6.8 Details of the main trials presented in the submission are summarised in Table 4.

¹¹ Mansour D, Verhoeven C, et al., (2011), 'Efficacy and tolerability of a monophasic combined oral contraceptive containing norgestrel acetate and 17 β -oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen', *Eur J Contracept Reprod Health Care*, 16(6):pp.430-43.

¹² Guang-Sheng F, Mei-Lu B, et al., (2010), 'Efficacy and safety of the combined oral contraceptive ethinylestradiol/drospirenone (Yasmin) in healthy Chinese women: a randomized, open-label, controlled, multicentre trial', *Clin Drug Investig*, 30(6):pp.387-96.

Table 4: Trials presented in the submission on primary efficacy of Yaz and Yasmin

Trial ID	Protocol title/ Publication title	Publication citation
Yaz (drospirenone 3 mg with ethinylestradiol 20 microgram) studies		
A12007	Bachmann G, Sulak PJ, et al. Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 micrograms ethinylestradiol and 3 mg drospirenone.	Contraception 2004; 70(3): 191-8
A30713	Hernádi L, Marr J, et al. Efficacy and safety of a low-dose combined oral contraceptive containing drospirenone 3 mg and ethinylestradiol 20 mcg in a 24/4-day regimen.	Contraception 2009; 80(1): 18-24
A29551	Anttila L, Kunz M, et al. Bleeding pattern with drospirenone 3 mg+ethinyl estradiol 20 mcg 24/4 combined oral contraceptive compared with desogestrel 150 mcg+ethinyl estradiol 20 mcg 21/7 combined oral contraceptive.	Contraception 2009; 80(5): 445-51
A09151	Klipping C, Marr J. Effects of two combined oral contraceptives containing ethinyl estradiol 20 microg combined with either drospirenone or desogestrel on lipids, hemostatic parameters and carbohydrate metabolism.	Contraception 2005; 71(6): 409-16
Yasmin (drospirenone 3 mg with ethinylestradiol 30 microgram) studies		
ME92052	A multicentre, open-labelled, randomized study on cycle control and tolerance of SH T 470 FA in comparison with Marvelon® in up to 26 cycles under long-term contraceptive use Foidart JM, Wuttke W, et al. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel.	1998 Eur J Contracept Reprod Health Care 2000; 5(2): 124-34
ME93044	Study of cycle control and tolerance of SH T 470 FA in comparison with Marvelon® in up to 2100 healthy women over 13 cycles of contraceptive use Huber J, Foidart JM, et al. Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone.	1998 Eur J Contracept Reprod Health Care 2000; 5(1): 25-34
96049B	An Open-Label, Multicentre Study to Evaluate the Efficacy and Safety of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 30 mg. Parsey KS, Pong A. An Open-Label, Multicenter Study to Evaluate Yasmin, a Low-Dose Combination Oral Contraceptive Containing Drospirenone, a New Progestogen.	1999 Contraception 2000; 61(2): 105-11
303121	Apter D, Borsos A, et al. Effect of an oral contraceptive containing drospirenone and ethinylestradiol on general well-being and fluid-related symptoms.	Eur J Contracept Reprod Health Care 2003; 8(1):37-51
Borenstein 2003	Borenstein J, Yu HT, et al. Effect of an oral contraceptive containing ethinyl estradiol and drospirenone on premenstrual symptomatology and health-related quality of life.	J Reprod Med 2003;48(2):79-85.
305511	Foidart JM, Sulak PJ, et al. Yasmin Extended Regimen Study Group. The use of an oral contraceptive containing ethinylestradiol and drospirenone in an extended regimen over 126 days.	Contraception 2006; 73(1):34-40

Source: Table 16, pp55-56 and Table 25, pp73-75 of the submission

6.9 The key features of the main trials are summarised in Table 5.

Table 5: Key features of the included evidence for Yaz and Yasmin

Trial	N	Design/duration	Bias	Treatment	Population	Outcome(s)
Yaz (drospirenone 3 mg with ethinylestradiol 20 microgram) studies						
Yaz vs. Mercilon (desogestrel 150 microgram with ethinylestradiol 20 microgram)						
A29551	453	R, parallel, OL, MC, 7 cycles	Unclear	Yaz 24/4 regimen ^a Mercilon 21/7 regimen ^b	Healthy women 18-35 y [^] , BMI ≤30	1: Pearl index, cycle control 2: Well-being, safety
A09151	60	R, OL 7 cycles	Unclear	Yaz 24/4 regimen ^a Mercilon 21/7 regimen ^b	Healthy women 18-35 y [^] , BMI ≤30	1: HDL- and LDL-cholesterol 2: Cycle control, contraceptive efficacy, safety
Yaz (no comparator)						
A12007	1,049	OL, MC 13 cycles	Unclear	Yaz 24/4 regimen ^a	Healthy women 17-36 y [^] , BMI ≤35	1: Contraceptive efficacy 2: Cycle control, safety
A30713	1,113	OL, MC 13 cycles	Unclear	Yaz 24/4 regimen ^a	Healthy women 18-35 y [^] , BMI ≤30	1: Pearl index 2: Well-being, safety
Yasmin (drospirenone 3 mg with ethinylestradiol 30 microgram) studies						
Yasmin vs. Marvelon (desogestrel 150 microgram with ethinylestradiol 30 microgram)						
ME92052	887	R, OL, MC 26 cycles (+3 mth f/up)	Unclear	Yasmin 21/7 regimen ^b Marvelon 21/7 regimen ^b	Healthy menstruating women 18-35 y [^]	1: Cycle control 2: Pearl Index, tolerance
ME93044	2,069	R, OL, MC 13 cycles (+6 wks f/up)	Unclear	Yasmin 21/7 regimen ^b Marvelon 21/7 regimen ^b	Healthy women 18-35 y [^]	1: Cycle control 2: Pearl Index, skin condition, safety
Yasmin (no comparator)						
96049B	333	OL, MC 13 cycles	Unclear	Yasmin 21/7 regimen ^b	Healthy women 18-35y [^] , ≤25% ideal body weight	Pearl Index, cycle control
303121	336	OL, MC 6 cycles	High	Yasmin 21/7 regimen ^b	18-40 y, somatic symptoms, PGWBI score 60-95	PGWBI, cycle control
Borenstein 2003	858	OL 2 cycles	High	Yasmin 21/7 regimen ^b	Women initiating Yasmin from gynaecologic health services	SF-12, Wellbeing (MDQ)
305511	184	OL, MC 2 cycles +18-36 wks	Unclear	Yasmin Run-in: 21/7 regimen ^b for 2 cycles Extended regimen: 1 tablet daily for 126 or 252 days	Healthy women 18-35y [^]	Contraceptive efficacy, cycle control, safety

Source: Table 16, pp55-56 and Table 25, pp73-75 of the submission, Foidart 2000, Huber 2000, Parsey 2000, Anttila 2009, Klipping 2005, Bachmann 2004, Hernádi 2009.

BMI = body mass index; f/up = follow up; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MC = multi-centre; MDQ = Moos Menstrual Distress Questionnaire; mth = month; OL = open label; PGWBI = Psychological General Well-Being Index; R = randomised, SF-12 = Medical Outcomes Short-Form-12; wk = week; y = years

[^] up to 30 years for smokers. Smokers >30 years were precluded due to age-dependent increased risk of arterial thrombosis among smokers using oral contraceptives.

^a 24x1 active tablets daily on days 1-24, then 4-day placebo tablets (or pill-free) from days 25-28 over the 28-day cycle.

^b 21x1 active tablet daily on days 1-21, then 7-day placebo tablets (or pill-free) from days 22-28 over the 28-day cycle.

6.10 Except for A29551, A09151, ME92052 and ME93044, which were randomised, open-label comparative trials, all other studies were open-label, non-comparative single arm design of Yaz and Yasmin. A29551 and A09151 randomised eligible patients to Yaz

or Mercilon for 7 cycles. ME92052 and ME93044 randomised patients to Yasmin or Marvelon for 13-26 cycles. A12007, A30713 were multi-centre, open-label single arm studies of Yaz over 13 cycles. Whereas 96049B, 303121, Borenstein and 305511 were open-label single arm studies of Yasmin for 2–13 cycles. Common efficacy outcomes across the trials included contraceptive efficacy assessed using Pearl Index or number of pregnancies and cycle control or bleeding pattern during treatment.

- 6.11 All included trials used TGA approved doses of Yaz and Yasmin, with the exception of 305511, which had two run-in cycles of Yasmin 21/7 dosing regimen (i.e. 21-day of active hormone tablets followed by 7-day placebo tablets (pill-free) over a 28-day cycle) followed by an extended regimen consisting of continuous daily active tablets (without pill-free intervals) for 126 days. Except for Borenstein 2003, the included studies enrolled menstruating women aged between 17-18 years and 30-40 years. Borenstein 2003 did not have age as eligibility criteria, and included women aged <18 years (n=22) and >35 years (n=128) (see Table 4).
- 6.12 The risk of bias for the trials of Yaz (A29551, A09151, A12007, A30713) and Yasmin (ME92052, ME93044, 96049B and 305511), with the exception of 303121 and Borenstein 2003, were considered unclear mainly due to studies being open-label and/or non-randomised. Therefore, patients were aware of their treatment allocation. Study 303121 and Borenstein 2003 were considered to be high risk of bias. The efficacy outcome in terms of contraceptive efficacy (i.e. number of pregnancies or Pearl Index) was an objective outcome. However, other patient outcomes such as the cycle control/bleeding pattern collected using diary cards and quality of life/wellbeing measures (e.g. Psychological General Well-Being Index (PGWBI) or Medical Outcomes Short-Form-12 (SF-12)) were subjective outcomes, and may be affected by reporting bias, particularly for within-group comparisons to baseline.
- 6.13 Baseline characteristics were generally balanced between treatment groups within the trials for Yaz (A29551, A09151) and Yasmin (ME92052, ME93044). However, there were some differences across the trials owing in part to differences in eligibility criteria, including:
- prior oral contraceptives: across the trials for Yaz (55.2% in A29551, 70.0-82.8% in A09151, 59.7% in A12007 and 63.6% in A30713) and Yasmin (69-73% in ME92052, 59.8-64.7% in ME93044, 54% in 96049B, none in Borenstein 2003, and not reported in 303121 and 305511).
 - intermenstrual bleeding: across the trials for Yaz (7.0-9.1% in A29551, 3.4-20.0% in A09151, 6.4% in A12007, 1.1% in A30713) and Yasmin (7-8% in ME92052, 6.3-6.6% in ME93044, and not reported in 96049B, 303121, Borenstein 2003 and 305511).
 - smoking history: across the trials for Yaz (27.6% in A29551, 28.8% in A09151, 25.6% in A12007 and 21.2% in A30713) and Yasmin (30.6-37.5% in ME93044, 13% in 96049B, 23.9% in 305511 and not reported in ME92042, 303121 and Borenstein 2003).

Comparative effectiveness

6.14 Table 6 presents the Pearl Index for the included trials of Yaz and Yasmin.

Table 6: Contraceptive efficacy for Yaz and Yasmin

Trials	Treatment			Comparator		
	n / cycles*	PI (UL 95%CI)	Adj PI [^] (UL 95%CI)	n / cycles*	PI (UL 95%CI)	Adj PI [^] (UL 95%CI)
	Yaz			Mercilon		
Study A29551 Yaz v Mercilon, 7 cycles	0 / 759	0 (3.40) ^a	0 (3.55)	1 / 756	0.93 (5.16)	0.93 (5.18)
Study A09151 Yaz v Mercilon, 7 cycles	0 / 908	0	0	0 / -	0	0
Study A12007 Yaz, 13 cycles	11 / 11,140	1.29 (2.30) ^a	0.72 (1.69)	NA	NA	NA
Study A30713 Yaz, 13 cycles	5 / 13,248	0.49 (1.14) ^a	0.22 (0.80)	NA	NA	NA
Pooled analysis Yaz, 7-13 cycles	16 / 26,055	0.80 (1.30)	0.41 (0.85)	-	-	-
Yasmin			Marvelon			
ME92052 Yasmin v Marvelon, 26 cycles	3 / 9,563	0.41 ^b	0	3 / 9,498	0.41	0
ME93044 Yasmin v Marvelon, 13 cycles	10 / 18,418	0.71 ^b	0.07	1 / 4,685	0.28	0.28
96049B Yasmin, 13 cycles	1 / 3,192	0.41 ^c	0	NA	NA	NA
Pooled analysis Yasmin, 13-26 cycles	14 / 31,173	0.57	0.09	-	-	-

Source: Tables 19 and 26 of the submission, pp58 and 77

CI = confidence interval; NA = not applicable; PI = Pearl index; UL = upper limit

Mercilon = desogestrel 150 microgram/ethinylestradiol 20 microgram; Marvelon = desogestrel 150 microgram/ethinylestradiol 30 microgram; Yaz = drospirenone 3 mg/ethinylestradiol 20 microgram; Yasmin = drospirenone 3 mg/ethinylestradiol 30 microgram.

* number of pregnancies / total treatment cycles

[^] adjusted Pearl Index accounts for pregnancies that are considered to have occurred due to factors other than method/user failure (e.g. noncompliance)

^a Pearl Index defined as number of pregnancies per 100 woman-years of exposure (i.e. cycles with back-up contraception, non-compliance, or missing information were excluded).

^b Pearl Index correcting for condom use (i.e. all pregnancies occurring under treatment were included in the numerator. All cycles in which at least 19 tablets were taken and in which no condom use was documented were included in the denominator).

^c The corrected Pearl Index was based on cycles without recorded use of other contraceptives.

6.15 Table 7 summarises the cycle control of Yaz and Yasmin from the included trials.

Table 7: Cycle control for Yaz and Yasmin in the included trials

Trials	Treatment		Comparator	
% Incidence spotting				
	n	Yaz	n	Mercilon
Study A29551 Yaz v Mercilon, 2-6 cycles	131-201/230*	57.1-87.5%	89-163/223*	40-73.3%
Study A09151 Yaz v Mercilon, 2-7 cycles	-	NR	-	NR
Study A12007 Yaz, 2-13 cycles	-	NR	-	N/A
	n	Yasmin	n	Marvelon
ME92052 Yasmin v Marvelon, 2-13 cycles	94	25.4%	83	22.7%
ME92052 Yasmin v Marvelon, 2-26 cycles	95	30.6%	102	32.5%
ME93044 Yasmin v Marvelon, 2-13 cycles	60-121/1,657*	3.62-7.33% / cycle	14-31/412*	3.46-7.69% / cycle
96049B Yasmin, 1-13 cycles (any cycle)	89	30^	-	N/A
% Incidence breakthrough bleeding				
	n	Yaz	n	Mercilon
Study A29551 Yaz v Mercilon, 2-7 cycles#	20-40/230*	8.8-17.3%	21-36/223*	9.4-16.3%
Study A09151 Yaz v Mercilon, 2-7 cycles	-	NR	-	NR
Study A12007 Yaz, 2-13 cycles	-	NR	-	N/A
	n	Yasmin	n	Marvelon
ME92052 Yasmin v Marvelon, 2-13 cycles	7	1.9%	7	1.9%
ME92052 Yasmin v Marvelon, 2-26 cycles	11	3.5%	11	3.5%
ME93044 Yasmin v Marvelon, 2-13 cycles	2-7/1,657*	0.11-0.43% / month	0-3/412*	0-0.78% / month
96049B Yasmin, 1-13 cycles (any cycle)	6	2%	-	N/A
% Incidence intermenstrual (spotting & breakthrough) bleeding				
	n	Yaz	n	Mercilon
Study A29551 Yaz v Mercilon, 2-7 cycles	-	NR	-	NR
Study A09151 Yaz v Mercilon, 2-7 cycles	-	NR	-	NR
Study A12007 Yaz, 2-13 cycles	≥883/1,027*	≥86%**	-	N/A
	n	Yasmin	n	Marvelon
ME92052 Yasmin v Marvelon, 2-13 cycles	45	12.2%	50	13.7%
ME92052 Yasmin v Marvelon, 2-26 cycles	42	13.5%	54	17.2%
ME93044 Yasmin v Marvelon, 2-12 cycles	507/1,657*	30.6%^	129/412*	31.4%^
96049B Yasmin, 1-13 cycles (any cycle)	56	19%	N/A	N/A
Mean duration of withdrawal bleeding (days)				
	n	Yaz	n	Mercilon
Study A29551 Yaz v Mercilon, 1-6 cycles	-	4.7-5.2 days	-	5.1-5.4 days
Study A09151 Yaz v Mercilon, 2-7 cycles	-	NR	-	NR
Study A12007 Yaz, 2-13 cycles	-	NR	-	N/A
	n	Yasmin	n	Marvelon
ME92052 Yasmin v Marvelon, 1-25 cycles	-	5 days	-	5 days
ME93044 Yasmin v Marvelon, 12 cycles	-	4.9 days (cycle 1) 4.6 days (cycle 12)	-	5 days (cycle 1) 4.6 days (cycle 12)
96049B Yasmin (per cycle)	-	4-7 days (71-83%)***	-	N/A

N/A = not applicable; NR = not reported

Mercilon = desogestrel 150 microgram/ethinylestradiol 20 microgram; Marvelon = desogestrel 150 microgram/ethinylestradiol 30 microgram; Yaz = drospirenone 3 mg/ethinylestradiol 20 microgram; Yasmin = drospirenone 3 mg/ethinylestradiol 30 microgram.

* Patient numbers not provided, and derived from percentages reported.

^ Any cycle.

Reported as unscheduled bleeding.

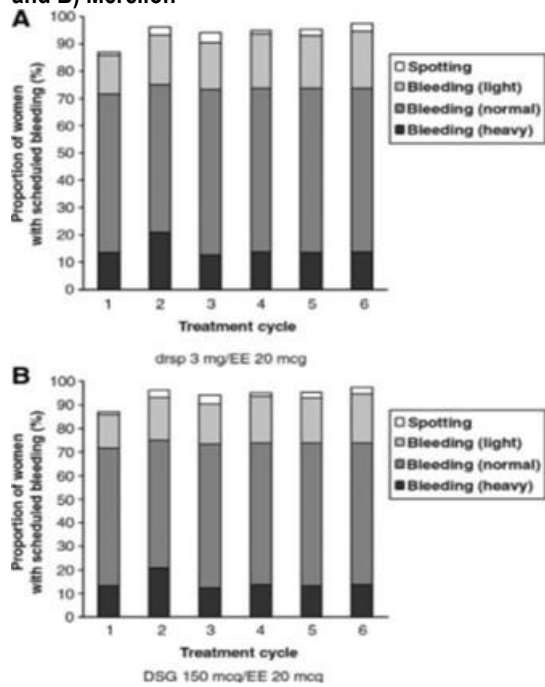
** proportion who experienced 3-5 bleeding/spotting episodes per reference period.

***majority of participants had a withdrawal bleed within this range.

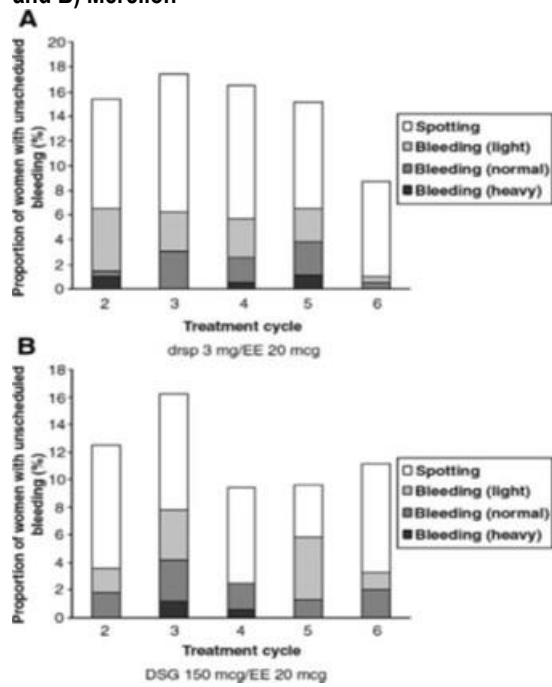
6.16 Figure 1 presents the cycle control with Yaz from three included trials (A29551, A09151, A12007). Figure 2 presents the cycle control with Yasmin from trials ME92052, ME93044 and 96049B.

Figure 1: Cycle control with Yaz from three included trials (A29551, A09151, A12007)

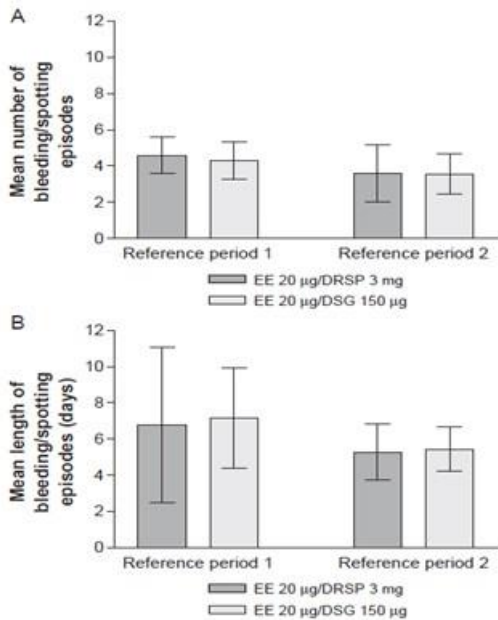
i) A29551 scheduled bleeding in cycles 1-6 for A) Yaz and B) Mercilon



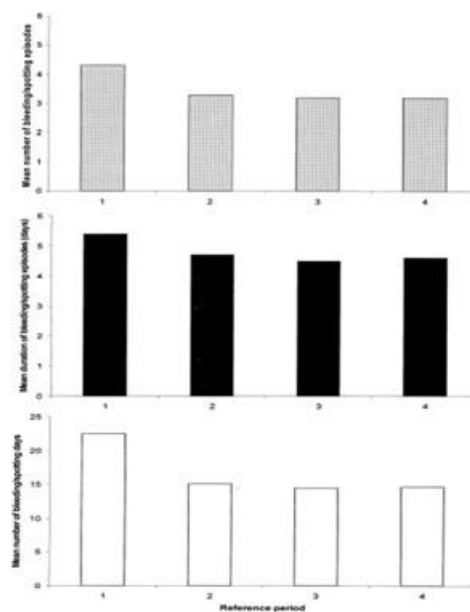
ii) A29551 unscheduled bleeding in cycles 2-6 in A) Yaz and B) Mercilon



iii) A09151 number (A) and duration (B) bleeding/spotting episodes during 90-day reference periods 1 and 2 for Yaz vs Marvelon (7 cycles)



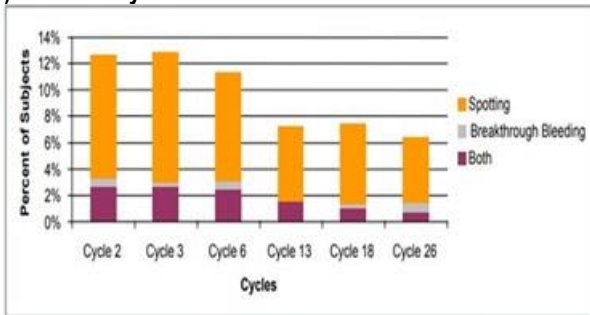
iv) A12007 number and duration of bleeding/spotting episodes during 90-day reference periods (13 cycles)



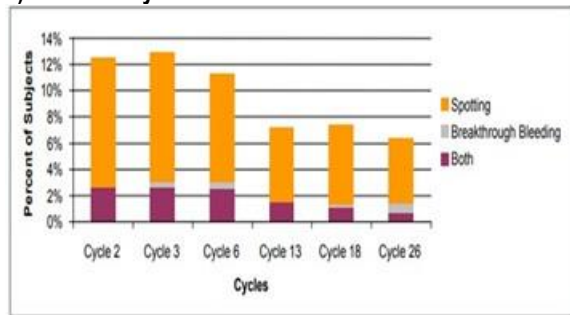
Source: Figure 33, p86 of the submission, Anttila 2009 (A29551), Kipling 2005 (A09151) and Bachmann 2003 (A12007).

Figure 2: Cycle control with Yasmin from trials ME92052, ME93044 and 96049B

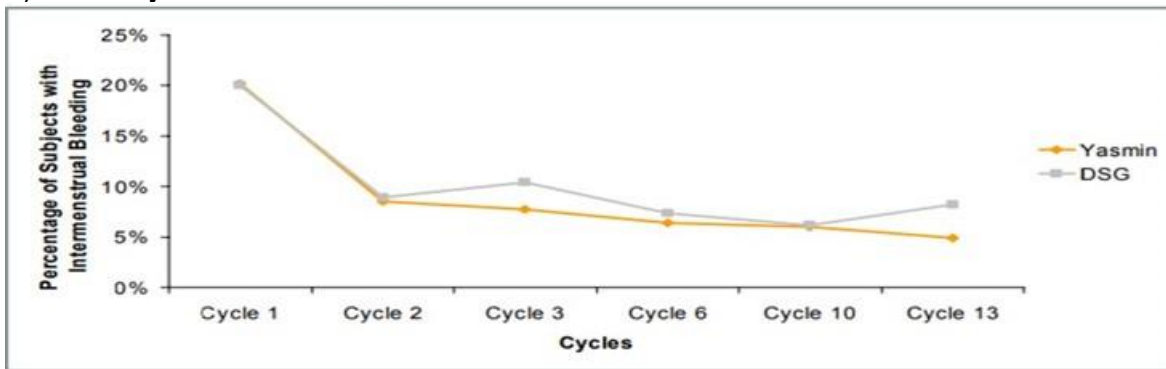
i) ME92052 cycle control with Yasmin



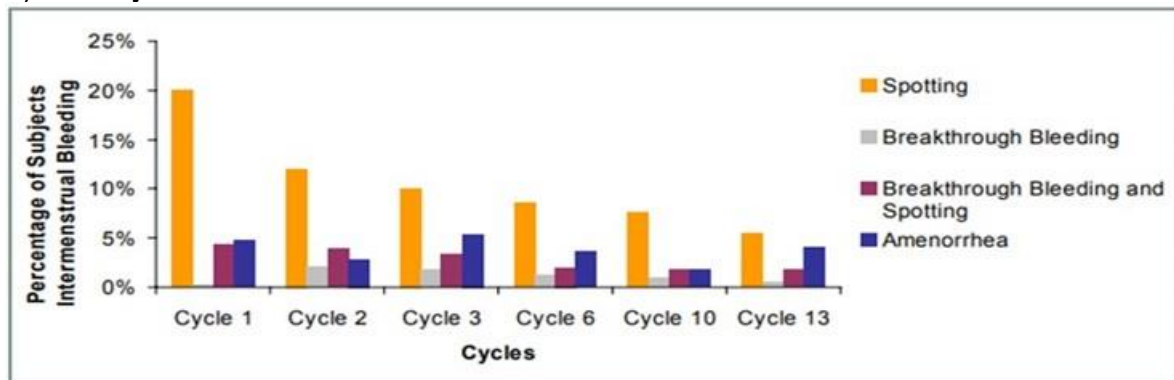
ii) ME92052 cycle control with Marvelon



iii) ME93044 cycle control with Yasmin vs Marvelon



iv) 96049B cycle control with Yasmin

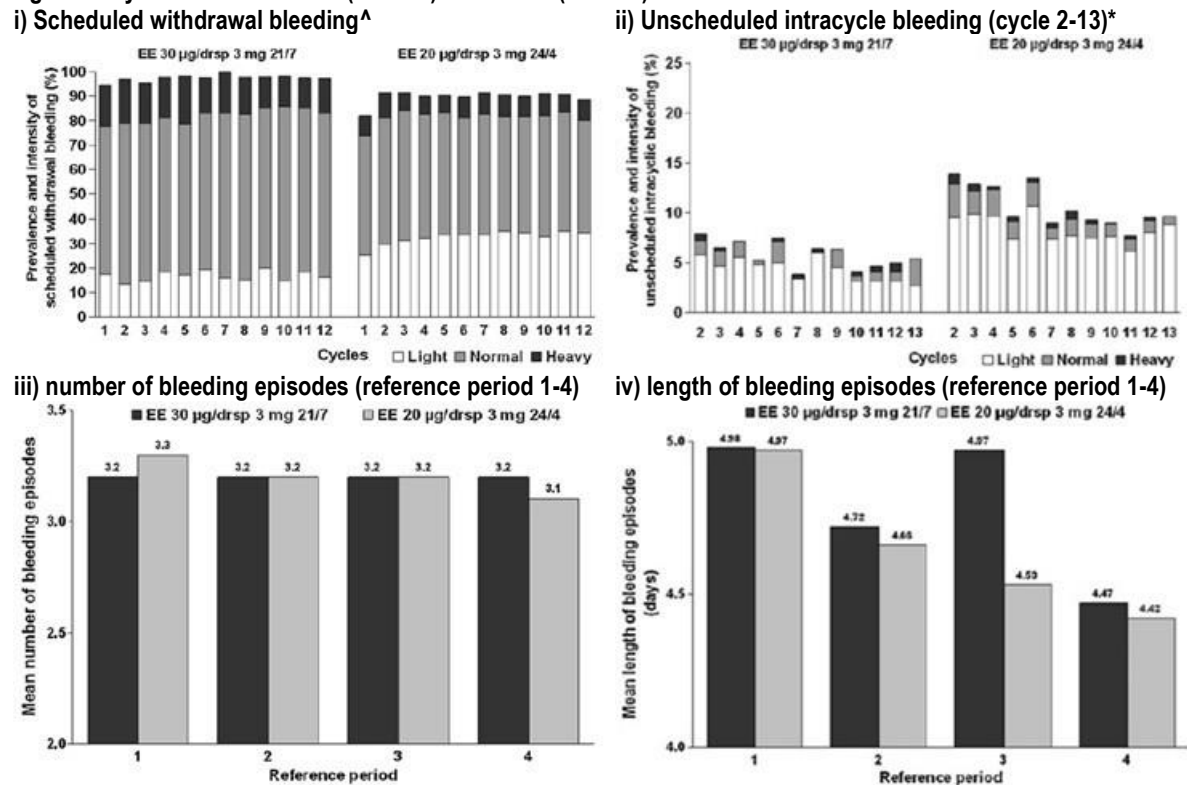


Source: Figures 17-20, pp67-68 of the submission.

6.17 The evaluation identified a study by Marr 2012¹³ comparing cycle control/bleeding pattern of Yaz vs Yasmin from A12007 and 96049B, respectively. This is presented in Figure 3.

¹³ Marr J, Gerlinger C, et al., (2012), 'A historical cycle control comparison of two drospirenone-containing combined oral contraceptives: ethinylestradiol 30 µg/drospirenone 3 mg administered in a 21/7 regimen versus ethinylestradiol 20 µg/drospirenone 3 mg administered in a 24/4 regimen', Eur J Obstet Gynecol Reprod Biol, 162(1):pp.91-5.

Figure 3: Cycle control with Yaz (A12007) vs Yasmin (96049B)



Source: Figure 1 and Figure 2, Marr 2012.

Yaz = drospirenone 3 mg/ethinylestradiol 20 microgram; Yasmin = drospirenone 3 mg/ethinylestradiol 30 microgram.

Note: the 90-day reference periods were defined by the World Health Organization. The first reference period started on the first day of treatment.

[^] Scheduled withdrawal bleeding episode was defined as the first bleeding/spotting that started following intake of the last active tablet in the current cycle up to five days before withdrawal of active treatment in the subsequent cycle (i.e. from day 22 of one cycle to day 17 of the subsequent treatment for Yasmin 21/7 regimen, or from day 25 to day 20, respectively for Yaz 24/4 regimen).

^{*} Unscheduled intracyclic bleeding episode was defined as all other bleeding episodes that did not fit the criteria for scheduled withdrawal bleeding.

6.18 Overall, the contraceptive efficacy as measured by the Pearl Index was generally comparable between Yaz and Yasmin and other COCs (i.e. Mercilon and Marvelon), and the Pearl Index was within the range for COCs (0.01-2.36). See Table 2 above. In addition, cycle control and bleeding patterns were comparable between Yaz and Mercilon as well as Yasmin and Marvelon. Compared to Yasmin, Yaz has a slightly higher Pearl Index and lower prevalence and intensity of withdrawal bleeding due to lower dose of ethinylestradiol.

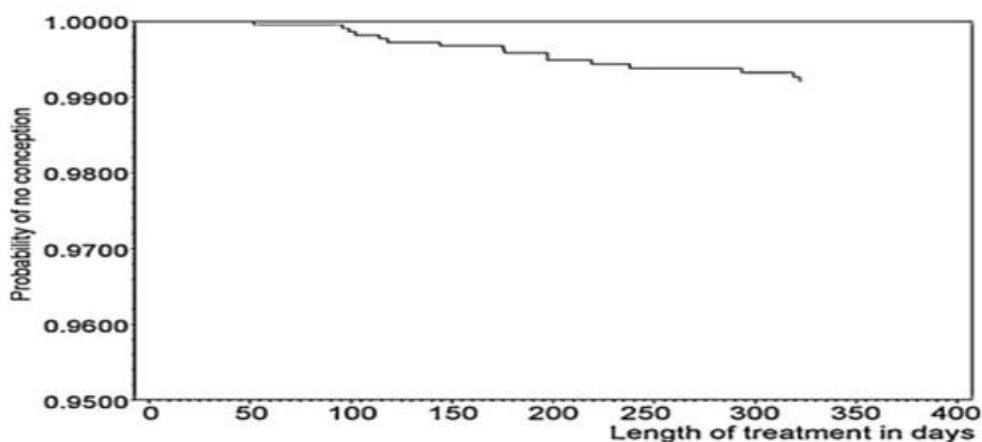
6.19 In summary, the results showed:

- **Yaz:** in A29551, the number of on-treatment pregnancies over 7 cycles was 0 in the Yaz group and 1 in the Mercilon group, with unadjusted Pearl Index (upper limit (UL) of the 95% confidence interval (CI)) of 0 (3.4) and 0.93 (5.16), respectively. In the pooled analysis of the four trials (A29551, A09151, A12007 and A30713) with a total of 2,386 women who received Yaz, there was a total of 16 pregnancies that occurred over 7 to 13 treatment cycles. The unadjusted and adjusted pooled Pearl Index (UL 95%CI) were 0.80 (1.30) and 0.41 (0.85),

respectively. The Kaplan–Meier estimate for the cumulative pregnancy rate after the last conception date was 0.0079 (95%CI: 0.0048, 0.0129) after up to 1 year of treatment, and the probability of contraceptive protection was estimated to be 99.21% (Figure 4). In A29551, most women (>50%) experienced ‘normal’ scheduled withdrawal bleeding in both Yaz and Mercilon groups in cycles 1-6. However, there was a trend towards spotting/light bleeding in the Yaz group compared to Mercilon. The incidence of intermenstrual or breakthrough bleeding was similar between groups and decreased from cycle 1 over cycles 2-6. Across trials A29551, A09151 and A12007, the mean number and duration of bleeding/spotting episodes and days was similar between Yaz and Mercilon and decreased over the 90-day reference periods with continuing treatment.

- **Yasmin:** In ME92052 and ME93044, contraceptive efficacy was similar between the Yasmin group and Marvelon group over 13 to 26 treatment cycles. In ME92052, there were three pregnancies in each group to 26 cycles, with a Pearl Index of 0.41 and adjusted Pearl Index of 0 in both groups. In ME93044, there were 10 pregnancies over 13 cycles in the Yasmin group (n=1657), with a Pearl Index of 0.71 and adjusted Pearl Index of 0.07 and 1 pregnancy in the Marvelon group (n=412), with an unadjusted and adjusted Pearl Index of 0.28. Across trials ME92052, ME93044 and 96049B, the pooled Pearl Index and adjusted Pearl Index for Yasmin was 0.57 and 0.09, respectively. Across the trials, there was a low incidence of intermenstrual bleeding (spotting and/or breakthrough bleeding), which were similar between Yasmin and Marvelon, with the highest incidence occurring in cycle 1 and decreasing onwards of cycle 2. In ME92052 and ME93044, the duration of withdrawal bleeding was similar between groups, between 4-7 days in the majority of cycles, with a trend towards shorter withdrawal bleeding with continuing treatment.
- In Marr 2012, cycle control/bleeding pattern was generally similar between Yaz (A12007) and Yasmin (96049B). However, there was a slightly lower mean proportion of scheduled withdrawal bleeding in the Yaz group (89.8%) compared to Yasmin (97.5%) over cycles 1-12. The proportion of unscheduled intermenstrual bleeding was low in both groups (10.7 and 5.9%, respectively). Most women experienced light or normal maximum intensity of scheduled withdrawal bleeding (83.8-90.7%) and unscheduled intermenstrual bleeding (light: 75.9-78.3%, normal: 17.3-17.7%). The mean duration of withdrawal bleeding was similar between Yaz and Yasmin and decreased from cycle 1 (4.6-5 days) to cycle 2 (4.5-5.1 days).

Figure 4: Kaplan–Meier estimate (days 52–322) based on the number of unintended pregnancies during treatment with Yaz in a 24/4 regimen pooled from the four included studies (A29551, A09151, A12007, A30713).



Source: Anttila et al, 2011

- 6.20 The PSCR claimed that the shorter hormone-free interval in the Yaz formulation may result in better suppression of ovarian follicular activity, which could lead to increased efficacy. The PSCR cited a study by Dinger et al which was a prospective, controlled, non-interventional long-term study investigating contraceptive effectiveness. After 1 year the contraceptive failure rate of ethinylestradiol 20 mcg/drospirenone 3 mg was 2.1% compared to 3.5% with the use of oral contraceptives containing other progestogens, and after 3 years the contraceptive failure rate was 4.7% versus 6.7% respectively.¹⁴
- 6.21 The contraceptive effectiveness of Yaz and Yasmin has been shown to be generally similar to other COCs and cycle control or bleeding pattern in different studies. The ESC considered that Yaz and Yasmin are equally effective to other COCs with regards to contraceptive effectiveness.
- 6.22 The submission presented patient-reported outcomes, including quality of life, for Yasmin from 303121 and Borenstein 2003. In 303121, there was improvement from baseline in the Psychological General Well-Being Index (PGWBI) score at cycles 3 and 6 ($p < 0.0001$). Investigator assessment of Clinical Global Impressions (CGI) scale showed 79.5% patients improved on Yasmin and 74.7% of patients reported satisfaction with the study drug. Borenstein 2003 showed in a before-after study that after treatment with Yasmin, there was improvement in mental component summary scale score ($p = 0.00$) on the SF-12 but not physical component summary scale score ($p > 0.05$). Further, Borenstein 2003 reported reduction in negative affect and water retention domains of the Menstrual Distress Questionnaire (MDQ) in all phases of the menstrual cycle after Yasmin treatment ($p < 0.05$). In 96049B women treated with Yasmin also showed some changes from baseline in items of the Women's Health

¹⁴ Dinger J, Minh TD, et al, (2011), 'Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen', *Obstet Gynecol*, 117(1):pp.33-40.

Assessment Questionnaire (WHAQ) (i.e. subset of the MDQ). This included reduction on negative effect and water retention in all menstrual phases ($p < 0.001$) to cycle 6 and reduction in severity of increased appetite in premenstrual ($p < 0.001$) and menstrual phases ($p = 0.001$). However, there was no change from baseline for impaired concentration, undesired hair change or feelings of well-being for any phase of the menstrual cycle.

- 6.23 In addition, the submission presented the effects of Yasmin on body weight and somatic symptoms. In ME92052, there was a reduction in mean body weight in the Yasmin group, whereas an increase in the Marvelon group over 26 cycles of treatment was observed. In ME93044, both groups showed a reduction in mean body weight that was significantly greater in the Yasmin group to cycles 8, after which there was a gradual regaining of weight. However, in ME92052 and ME93044, the majority of women treated with Yasmin and Marvelon maintained stable body weight within 2 kg of their baseline. Study 303121 showed that women treated with Yasmin experienced a reduction from baseline in the incidence and severity of somatic symptoms at cycle 6, including abdominal bloating ($p < 0.001$), breast tenderness ($p < 0.001$) and swelling of extremities ($p = 0.597$).
- 6.24 The submission also presented results from study 305511 and Foidart 2006 for the extended treatment regimen with Yasmin up to 126 days (18 weeks), which showed that approximately 40% had complete absence of bleeding and 60% had at least one unscheduled (breakthrough) bleeding. The bleeding was predominantly light in intensity (31.6% maximum light bleeding, 24.3% normal and 5.6% heavy bleeding). However, the submission is not seeking TGA registration nor PBS listing for the extended treatment regimen of Yasmin.

Comparative harms

- 6.25 Table 8 summarises the key adverse events (AEs) for across the main trials for Yaz (A29551, A09151, A12007 and A30713) and Yasmin (ME92052, ME93044 and 96049B).

Table 8: Adverse events in the main trials for Yaz and Yasmin.

AEs	A29551 n(%)		A09151 n(%)		A12007 n(%)	A30713 n(%)	ME92052 n(%)		ME93044 n(%)		96049B n(%)
	Yaz N=229	Mercilon N=220	Yaz N=29	Mercilon N=30	Yaz N=1027	Yaz N=1101	Yasmin N=442	Marvelon N=445	Yasmin N=1657	Marvelon N=412	Yasmin N=326
Any AEs	150 (65.5)	124 (56.4)	29 (100)	28 (93.3)	949 (92.4)	526 (47.8)	327 (73.9)	346 (77.8)	-	-	230 (70.6)
Discontinuation due to AEs	18 (7.9)	9 (4.1)	3 (10.3)	2 (6.7)	77 (7.5)	52 (4.7)	48 (10.9)	4 (0.9)	146 (8.8)	28 (6.9)	20 (6.1)
Drug-related AEs ^a	59 (25.8)	34 (15.5)	17 (58.6)	13 (43.4)	395 (38.5)	233 (21.2)	188 (42.5)	187 (42.0)	638 (38.5)	133 (32.3)	-
Common AEs											
Acne	1 (0.4)	5 (2.2)	2 (6.9)	2 (6.7)	12 (1.2)	6 (0.5)	5 (1.1)	10 (2.2)	-	-	-
Breast pain	3 (1.3)	0 (0)	2 (6.9)	0	65 (6.3)	14 (1.3)	53 (12.0)	41 (9.2)	106 (6.4)	19 (4.6)	28 (8.6)
Breast tenderness	6 (2.6)	1 (0.5)	-	-	-	-	-	-	-	-	-
Dysmenorrhoea	3 (1.3)	2 (0.9)	2 (6.9)	2 (6.7)	12 (1.2) ^a	-	12 (2.7) ^a	16 (3.6) ^a	36 (2.2)	9 (2.2)	-
Headache	7 (3.1)	6 (2.7)	5 (17.2)	2 (6.7)	67 (6.5)	31 (2.9)	48 (10.9)	60 (13.5)	162 (9.8)	26 (6.3)	16 (4.9)
Metrorrhagia	6 (2.6)	6 (2.7)	NR	NR	12 (1.2)	89 (8.0)	-	-	-	-	-
Amenorrhoea	-	-	-	-	-	50 (4.5)	-	-	-	-	-
Mood swings	3 (1.3)	1 (0.5)	2 (6.9)	4 (13.3)	12 (1.2)	-	-	-	-	-	-
Nausea	4 (1.7)	3 (1.4)	0	2 (6.7)	26 (2.5)	12 (1.1)	21 (4.8)	16 (3.6)	70 (4.2)	7 (1.7)	-
Decreased libido	-	-	-	-	11 (1.1)	2 (0.2)	-	-	-	-	-

Source: Table 33 and Table 34, pp88-90 of submission main body, Anttila 2009 (A29551), Kippling 2005 (A09151), Bachmann 2004 (A12007), Hernadi 2009 (A30713), Foidart 2000 (ME92052), Huber 2000 (ME93044), Parsey 2000 (96049B).

AE = adverse event; NR = not reported

^a AEs classified as treatment related (possible/probable/definite)

^a reported as abdominal pain

6.26 Overall, the incidence of any AEs was similar between the treatment arms for Yaz vs Mercilon to cycle 7 and Yasmin vs Marvelon to cycles 13-26. The majority of AEs were mild to moderate in intensity and typical of those associated with hormonal contraceptive treatment. In A29551 and A09151 for Yaz, patients treated with Yaz had numerically more discontinuations due to AEs and treatment-related AEs (possibly, probably and definitely related to treatment) compared to Mercilon. In ME92052 and ME93044, patients treated with Yasmin had numerically more discontinuations due to AEs compared to Marvelon, however treatment-related AEs were generally similar between groups.

6.27 Across the trials for Yaz and Yasmin, the most frequently reported AEs (occurring in ≥1% of women) included headaches, breast pain, mood swings/emotional lability, dysmenorrhoea, metrorrhagia and nausea.

Venous thromboembolism

- 6.28 The use of any combined hormonal contraceptive increases the risk of VTE compared with no use. Yaz and Yasmin are contraindicated if a woman has risk factors that put her at high risk of VTE.
- 6.29 An analysis of the United States FDA’s Adverse Event Reporting System found that venous thrombotic events were reported approximately five times more frequently with drospirenone-containing COCs compared to levonorgestrel-containing COCs.¹⁵
- 6.30 The Therapeutic Guidelines¹⁶ state that COCs containing drospirenone (along with cyproterone, desogestrel and gestodene) might have a slightly higher risk of VTE compared to COCs containing levonorgestrel or norethisterone. The estimated annual incidence of VTE per year of use is 9-12 out of 10,000 females for drospirenone compared to 2 out of 10,000 females of reproductive age who are not using COCs or pregnant, and 5-7 out of 10,000 females using a COC with levonorgestrel or norethisterone.
- 6.31 The submission presented longer-term safety data from the European Active Surveillance study (EURAS, Heinemann and Dinger 2004¹⁷), which was a prospective, controlled cohort study of patients using drospirenone/ethinylestradiol (Yasmin), levonorgestrel-containing oral contraceptives and other oral contraceptives with progestogens. Heinemann and Dinger 2004 reported no major differences between the groups on the rates of overall serious adverse effects, organ-system specific serious adverse effects, overall mortality, outcome-specific mortality, overall cancer and organ system-specific cancer. The incidence of all VTE events were also similar between Yasmin, levonorgestrel-containing oral contraceptives and other oral contraceptives. The hazard ratios (95%CI) for VTE risks using Cox regression analysis for Yasmin vs levonorgestrel and other oral contraceptives was 1 (95%CI 0.43, 2.29) and 0.86 (95%CI 0.4, 1.85), respectively. The majority of VTEs (90.5%) occurred in users who switched from another oral contraceptive. The rates of VTE are usually highest during the first year of use, with approximately 3-fold more VTEs reported after the first year compared to 3 years of follow-up. Further, obese women (body mass index (BMI) ≥ 30) had more than 4-fold higher VTE risk compared to women with normal weight (BMI 20.0-24.9).

¹⁵ Madigan D, Shin J, (2018), ‘Drospirenone-containing oral contraceptives and venous thromboembolism: an analysis of the FAERS database’, *Open Access J Contracept*, 9:pp.29-32.

¹⁶ Therapeutic Guidelines Australia (eTG), (2020), ‘Choice of contraceptive method: contraception and venous thromboembolism’. Therapeutic Guidelines Limited, www.tg.org.au

¹⁷ Dinger J, Heinemann LA, (2007), ‘The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation’, *Contraception*, 75(5):pp.344-54.

- 6.32 In 2011 the TGA reviewed information available and assessed the risk of VTE occurring with the use of drospirenone-containing oral contraceptives.¹⁸ It noted that the published studies suggested a two- to three-fold increase in the risk of VTE in women taking COCs with drospirenone compared to women taking COCs with levonorgestrel. The TGA also noted there were a number of limitations in these studies. The TGA noted all oral contraceptives pose a small risk of VTE. This risk is influenced by age, family history and lifestyle factors such as weight and smoking status. No regulatory action was ultimately taken by the TGA to remove or restrict sales of Yaz or Yasmin.
- 6.33 A systematic review and meta-analysis, conducted in 2014-2015 by Bateson 2016¹⁹, found no increased risk of VTE with the use of drospirenone-containing COCs compared to levonorgestrel or other COCs in prospective (including EURAS study) or case control studies. However, an increased risk was seen in retrospective cohort and nested case control studies. Another systematic review by Dragoman 2018²⁰ found that COCs containing drospirenone, cyproterone acetate, desogestrel or gestodene were associated with a significantly increased risk of VTE compared to levonorgestrel-containing COCs (pooled risk ratio 1.5-2.0). The estimated risks were only slightly attenuated (compared with the overall analysis) when the analyses were restricted to monophasic COCs containing 30 microgram ethinylestradiol and desogestrel, drospirenone or gestodene, compared with levonorgestrel.
- 6.34 The ESC noted that the use of COCs is associated with an increased risk of VTE, however the absolute risk of VTE in individuals who use COCs is small. The risk depends on the dose of estrogen, the dose and type of progestogen and the presence of other risk factors, and is highest in the first year of use (including when the COC is restarting after a break of ≥ 1 month). The ESC noted the incidence of VTE per 10,000 women has been estimated to be 5-7 for COCs containing levonorgestrel or norethisterone with ≤ 35 micrograms ethinylestradiol, and 9-12 for COCs containing drospirenone with ethinylestradiol.

Benefits/harms

- 6.35 The submission did not present comparative efficacy and safety data to allow for quantitative comparison of the benefits and harms of treatment between Yaz and Yasmin and other PBS-listed oral contraceptives. Accordingly, a benefits and harms table was not presented.
- 6.36 The ESC noted that the majority of COCs contain ethinylestradiol as the estrogen, which is the estrogen in Yaz and Yasmin as well as in the COCs currently PBS-listed.

¹⁸ Therapeutic Goods Administration, (2011), 'Oral contraceptives containing drospirenone (Yaz and Yasmin), www.tga.gov.au/news/safety-alerts/oral-contraceptives-containing-drospirenone-yaz-and-yasmin

¹⁹ Bateson D, Butcher BE, et al., (2016), 'Risk of venous thromboembolism in women taking the combined oral contraceptive: A systematic review and meta-analysis', *Aust Fam Physician*, 45(1):pp.59-64.

²⁰ Dragoman MV, Tepper, NK, et al., (2018), 'A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception', *Int J Gynecol Obstet*, 141:pp.287-294.

The ESC considered that while the COCs contain different progestogens, the main difference between the progestogens is the risk of VTE, and there are also differences in androgenic activity. There is a lower risk of VTE associated with the progestogens levonorgestrel and norethisterone (which are in the COCs currently PBS-listed) compared to drospirenone (which is in Yaz and Yasmin).

Clinical claim

- 6.37 The submission did not make a direct clinical claim.
- 6.38 The submission described the effectiveness of Yaz as acceptable in terms of contraceptive efficacy. Yaz has acceptable safety, with similar AEs compared to Mercilon and were typical of those associated with use of a hormonal contraceptive.
- 6.39 The submission described Yasmin as effective in terms of contraceptive efficacy, cycle control and patient-reported outcomes of quality of life and wellbeing. Yasmin has similar safety and tolerability to other COCs (including Marvelon).
- 6.40 Based on the evidence provided, the effectiveness of Yaz and Yasmin and other COCs (e.g. Mercilon and Marvelon) were generally similar in terms of contraceptive efficacy and cycle control/bleeding pattern. The incidence of AEs was generally similar between Yaz and Yasmin and the safety profile of other COCs, however there was potential for increased risk of VTE with drospirenone-containing COCs.
- 6.41 The PSCR claimed that drospirenone has a number of benefits compared to other progestogens in COCs due to its anti-mineralocorticoid effects leading to reduced weight and blood pressure, and therefore potential cardiovascular benefits. The PSCR claimed that most other synthetic progestogens do not have anti-mineralocorticoid effects, which may lead to weight gain and increased blood pressure.
- 6.42 The PSCR included an additional reference by Oelkers et al to support the claim that drospirenone has the potential to reduce cardiovascular morbidity.²¹
- 6.43 However, the paper by Oelkers was a short review of drospirenone, and stated slight reductions in weight and blood pressure are surrogate parameters for avoiding or preventing cardiovascular complications. The ESC considered the paper by Oelkers was insufficient to support the claim that drospirenone could reduce cardiovascular morbidity. No direct evidence was provided to demonstrate that Yaz or Yasmin led to a reduction in cardiovascular risk.
- 6.44 The ESC noted the submission did not make a clinical claim. It noted that progestogens in COCs differed in their androgenic activity, and that drospirenone has anti-mineralocorticoid and anti-androgenic activity, however considered that there is no compelling evidence that lower or anti-androgenic activity provides any clinical

²¹ Oelkers W, (2004), 'Drospirenone, a progestogen with antiminerlocorticoid properties: a short review', *Mol Cell Endocrinol*, 217(1-2):pp.255-61.

advantages. The ESC further noted that there is a lack of evidence to demonstrate the claimed anti-mineralocorticoid activity provides clinical benefits.

- 6.45 The pre-PBAC response referenced an additional study of 80 women who received either ethinylestradiol 30 micrograms, 20 micrograms or 15 micrograms with 3 mg drospirenone, or ethinylestradiol 30 micrograms plus 150 micrograms levonorgestrel. After 6 months, the women receiving a combination with drospirenone had a reduction in systolic and diastolic blood pressure by 1-4 mmHg, whereas there was a 1-2 mmHg increase in women taking ethinylestradiol/levonorgestrel. There was also a mean reduction in body weight of 0.8-1.7 kg in women taking a COC with drospirenone, compared to a 0.7 kg increase in women using ethinylestradiol/levonorgestrel.²² The pre-PBAC response claimed that COCs containing drospirenone were preferred for use in women with hypertension, and that listing Yaz and Yasmin on the PBS would provide more options of COCs for women at different life stages. The Therapeutic Guidelines recommends addressing other causes if weight gain is experienced when taking COCs, and do not recommend one COC compared to another if this adverse effect is experienced. The Therapeutic Guidelines also contraindicates combined hormonal contraception in hypertension (≥ 160 mmHg systolic blood pressure, ≥ 100 mmHg diastolic).
- 6.46 The pre-PBAC response provided 5 letters of support for the PBS listing of Yaz and Yasmin – one letter from Family Planning Australia and 4 from individual clinicians. The letters noted the value of having multiple COC options available on the PBS to provide alternative options if patients experience adverse effects to other COCs, as well as the non-contraceptive benefits of Yaz and Yasmin for conditions such as acne and PMDD.
- 6.47 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.
- 6.48 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

Economic analysis

- 6.49 The submission did not provide an economic analysis.
- 6.50 The PBAC noted the submission did not provide an economic analysis, therefore there was no basis for assessing cost-effectiveness.
- 6.51 The submission requested the following dispensed price for maximum quantity (DPMQ) and approved ex-manufacturer price (AEMP) for Yaz and Yasmin:

²² Oelkers W, Foidart JM, Dombrovicz N, et al., (1995), 'Effects of a new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism', *J Clin Endocrinol Metab*, 80(6):pp.1816-21.

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- DPMQ of \$| and AEMP of \$| for Yaz 28 tablets and Yasmin 28 tablets x 1 pack;
- DPMQ of \$| and AEMP of \$| for Yaz 28 tablets and Yasmin 28 tablets x 3 packs.

6.52 The requested DPMQs equate to \$█ per tablet for the 1 x 28 tablets pack, and \$| per tablet for the 3 x 28 tablets pack.

6.53 Other COCs currently listed on the PBS have the following DPMQs (Table 9):

Table 9: DPMQs of PBS-listed COCs

Item	Brand	DPMQ*	DPMQ/tablet**
levonorgestrel 100 microgram + ethinylestradiol 20 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Femme-Tab ED 20/100	\$19.10	\$0.17
levonorgestrel 125 microgram + ethinylestradiol 50 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Microgynon 50 ED	\$22.86	\$0.20
levonorgestrel 150 microgram + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Eleanor 150/30 ED Evelyn 150/30 ED Femme-Tab 30/150 ED Lenest® 30 ED Micronelle® 30 ED	\$17.40	\$0.16
	Levlen ED	\$21.47	\$0.19
levonorgestrel 50 microgram + ethinylestradiol 30 microgram tablet [6] (& levonorgestrel 75 microgram + ethinylestradiol 40 microgram tablet [5] (& levonorgestrel 125 microgram + ethinylestradiol 30 microgram tablet [10] (& inert substance tablet [7], 4 x 28	Logynon ED Trifeme 28	\$20.71	\$0.19
	Triquilar ED	\$34.27	\$0.31
norethisterone 1 mg + ethinylestradiol 35 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Norimin-1 28 Day	\$18.97	\$0.17
norethisterone 500 microgram + ethinylestradiol 35 microgram tablet [21] (& inert substance tablet [7], 4 x 28	Norimin 28 Day	\$18.97	\$0.17

Source: PBS website

DPMQ = dispensed price for maximum quantity

*DPMQ as of April 2024

**Rounded to 2 decimal places

6.54 The submission noted that the requested DPMQ and AEMP prices for Yaz and Yasmin are higher than those of oral contraceptives currently listed on the PBS. It claimed that the prices requested were reasonable for the following reasons:

- The DPMQ prices requested were lower or consistent with the prices currently paid for private prescriptions for these products in Australia;
- The AEMPs requested were lower than the prices offered to similar markets overseas; and
- The AEMPs requested were slightly higher than the cost of goods.

6.55 The submission provided a comparison of the requested AEMPs and DPMQs with the cost of private prescriptions and total cost of goods for these items (Table 10).

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Table 10: Comparison of requested DPMQs, AEMPs, cost of private prescription and total cost of goods for Yaz and Yasmin

Item	Requested DPMQ	Requested AEMP	Cost private prescription*	Total cost of goods
Drospirenone 3 mg & ethinylestradiol 20 microgram tablets [21] & inert substance tablets [7] x 1 pack	\$█	\$█	\$25.95 - \$29.99	\$█
Drospirenone 3 mg & ethinylestradiol 20 microgram tablets [21] & inert substance tablets [7] x 3 packs	\$█	\$█	\$68.95 - \$79.99	\$█
Drospirenone 3 mg & ethinylestradiol 30 microgram tablets [21] & inert substance tablets [7] x 1 pack	\$█	\$█	\$27.99 - \$29.99	\$█
Drospirenone 3 mg & ethinylestradiol 30 microgram tablets [21] & inert substance tablets [7] x 3 packs	\$█	\$█	\$67.95 - \$79.99	\$█

Source: Tables 30 and 32 of submission main body, pp.84,86

AEMP=approved ex-manufacturer price, DPMQ=dispensed price for maximum quantity

*Cost of private prescriptions as of 5 March 2024 from different pharmacy banner groups

6.56 The submission provided a comparison of the requested AEMPs with that of other markets overseas (see Table 11).

Table 11: Comparison of proposed AEMP with other markets overseas

Item	Proposed AEMP	Austria	Canada	Germany	Ireland	Spain	Switzerland	Taiwan
Drospirenone 3 mg & ethinylestradiol 20 microgram tablets [21] & inert substance tablets [7] x 1 pack	\$█		\$█			\$█		
Drospirenone 3 mg & ethinylestradiol 20 microgram tablets [21] & inert substance tablets [7] x 3 packs	\$█					\$█		
Drospirenone 3 mg & ethinylestradiol 30 microgram tablets [21] & inert substance tablets [7] x 1 pack	\$█	\$█	\$█	\$█	\$█	\$█		
Drospirenone 3 mg & ethinylestradiol 30 microgram tablets [21] & inert substance tablets [7] x 3 packs	\$█	\$█		\$█		\$█		

Source: Table 31, p85 of submission main body

Note: Blank space means pricing not available as brand not supplied in this country. The indicated AUD price for each market is the EURO to AUD conversion at the 1.69 AUD = 1 EURO

AEMP=approved ex-manufacturer price

Shading identifies AEMPs lower than the AEMP requested in the submission

- 6.57 Under Section 101 (3B) of the *National Health Act*, the PBAC is not able to recommend to the Minister that a drug or medicinal preparation be made available as a Pharmaceutical Benefit if it is substantially more costly than an alternate therapy or therapies unless for some patients, it provides a significant improvement in efficacy or reduction of toxicity over the alternate therapy or therapies.
- 6.58 Any of the COCs currently PBS-listed could be considered alternative therapies. No evidence was provided that Yaz or Yasmin provide a significant improvement in efficacy and/or reduction in toxicity compared to alternative COCs currently listed on the PBS.
- 6.59 The ESC considered the evidence provided did not sufficiently demonstrate that Yaz or Yasmin offered a significant improvement in efficacy or reduction in toxicity compared to other COCs currently listed on the PBS. The ESC noted that other PBS-listed COCs contain the progestogens levonorgestrel or norethisterone, which have a lower risk of VTE compared to drospirenone in Yaz and Yasmin.

Drug cost/patient/year: \$ [REDACTED]

- 6.60 The estimated drug cost/patient per year would be \$ [REDACTED] for both Yaz and Yasmin, 3 x 28 tablets pack, based on a DPMQ of \$ [REDACTED] and 4.35 prescriptions per year.
- 6.61 If the 1 x 28 tablets pack was used, the estimated drug cost/patient per year would be \$ [REDACTED] for both Yaz and Yasmin, based on a DPMQ of \$ [REDACTED] and 13.04 prescriptions per year.
- 6.62 Table 12 outlines the cost per patient per year for Yaz and Yasmin 1 x 28 tablets pack and 3 x 28 tablets pack compared to COCs currently PBS-listed.

Table 12: Drug cost per patient per year for proposed and comparator drugs

	Proposed drug Model (3 x 28 tablets pack)	Proposed drug Model (1 x 28 tablets pack)	Proposed drug Financial estimates	Comparator Model*	Comparator Model**	Comparator Financial estimates
Mean dose	1 tablet daily	1 tablet daily	1 tablet daily	1 tablet daily	1 tablet daily	1 tablet daily
Mean duration	Continuous	Continuous	Continuous	Continuous	Continuous	Continuous
Cost/patient/month	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED] - \$ [REDACTED]	\$4.73	\$9.31	\$4.73 - \$9.31
Cost/patient/year	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED] - \$ [REDACTED]	\$56.74	\$111.76	\$56.74 - \$111.76

Source: Based on information provided in submission main body and PBS website (www.pbs.gov.au) as of April 2024

*Based on lowest cost PBS-listed COC (levonorgestrel 150 microgram + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 4 x 28) with a DPMQ of \$17.40 for 112 tablets

**Based on highest cost PBS-listed COC (levonorgestrel 50 microgram + ethinylestradiol 30 microgram tablet [6] (& levonorgestrel 75 microgram + ethinylestradiol 40 microgram tablet [5] (& levonorgestrel 125 microgram + ethinylestradiol 30 microgram tablet [10] (& inert substance tablet [7], 4 x 28), Triquilar ED (has a brand price premium)

Estimated PBS usage & financial implications

- 6.63 This submission was not considered by DUSC.
- 6.64 The submission stated that it used a modified epidemiological approach to estimate the PBS usage and financial implications for Yaz and Yasmin on the PBS. The submission used market data (units sold) to estimate utilisation, given that both Yaz and Yasmin have been available on the private market. This would be more accurately

described as a market share approach, informed by private market data, with patient numbers back-calculated from supply.

- 6.65 The submission stated that in the past 20 years usage of COCs has been declining as other methods of contraception (e.g. long-acting reversible contraceptives such as intrauterine devices, implants) have become available (Figure 5). The market trend for both Yaz and Yasmin has followed this decline. The submission’s estimated PBS usage of both products reflects this, with estimated continued decline in usage over Years 1-6. The submission estimated this decline would be slower if Yaz and Yasmin are listed on the PBS and they become more affordable to patients (Figure 6), but the market would remain in decline. This contrasted with the claimed need for newer generation COCs and that Yaz/Yasmin would be more affordable to more patients if listed on the PBS.

Figure 5: Total oral contraceptive and long-acting reversible contraceptives market volume change over the last 2 years

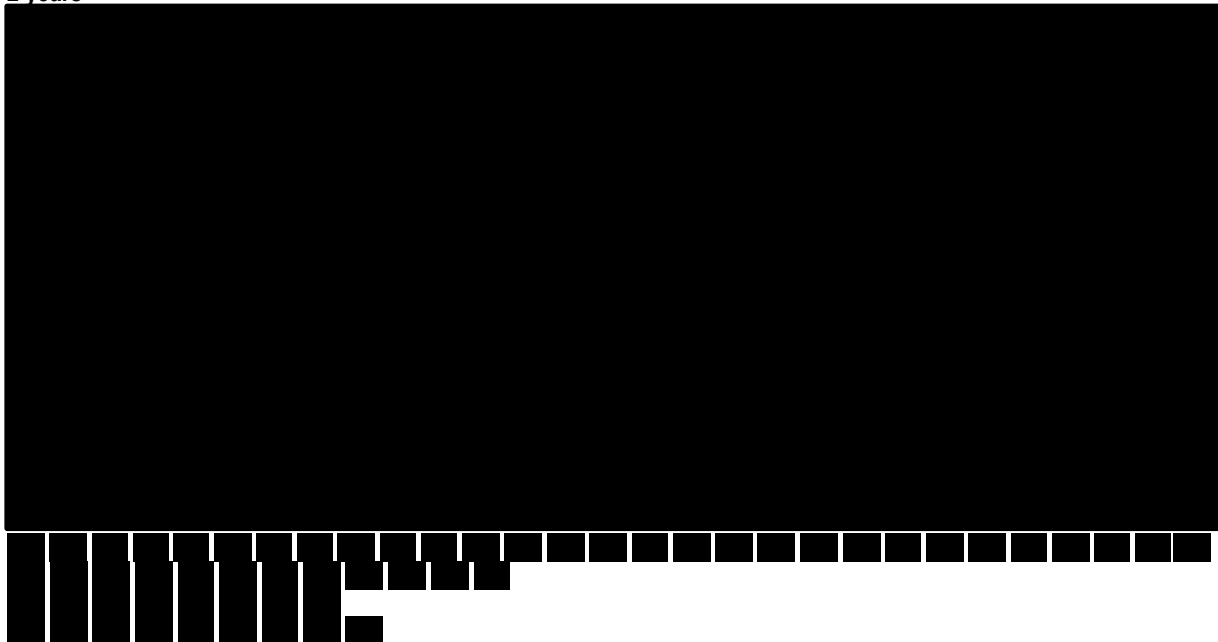


Figure 6: Monthly volume trend of Yaz and Yasmin



- 6.66 The submission stated that the sponsor does not actively promote these products, and claimed that if Yaz and Yasmin are PBS-listed uptake is not expected to increase significantly. This did not account for public interest, including that of clinicians and patients, if Yaz and Yasmin are PBS-listed as newer generation COCs.
- 6.67 The submission estimated a split of [REDACTED]% usage of the 1-month pack and [REDACTED]% usage of the 3-month pack for both Yaz and Yasmin combined, based on IMS data from the previous 5 years.
- 6.68 Table 13 outlines key inputs for financial estimates.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent population	Initial patient numbers based on 100% of patients currently using products.	Likely appropriate as a starting point, however this did not account for people on other private COCs who may switch to a subsidised product. Additionally, people using other COCs listed on the PBS may switch to Yaz and Yasmin. Therefore, the number of people treated with Yaz and Yasmin was likely underestimated.
% who meet other PBS criteria	100%	Requested unrestricted PBS listing.
Growth rate	-2% in Year 1 decreasing to -6.5% in Year 6. Based on trend in decreasing use of COCs, with a slower decline to current trend as PBS listings will make products more affordable.	Uncertain. While the estimates accounted for declining use in COCs and a slower decline if products are PBS-listed due to being more affordable, there was no further explanation for the quantum.
Compliance rate	100%	Likely appropriate. Advice in Product Information is that if a tablet is missed, the patient should take the tablet as soon as remembered.
Grandfathered patients	Nil.	Submission included a number of “Grandfathered” patients. However, as the requested listings were unrestricted PBS listings and patients currently using these products would be able to access these if PBS-listed, no Grandfather arrangements would be required.
Dose/duration	1 tablet daily ongoing.	Appropriate.
Offsets for comparator	Not included.	Submission did not account for patients currently using PBS listed COCs and hormonal contraceptives who would switch to Yaz or Yasmin if they become PBS-listed. Given the requested price was higher than the DPMQs of the existing listings, this would underestimate the total cost to the PBS/RPBS.

Source: Submission main body

COC = combined oral contraceptive; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; DPMQ = dispensed price for maximum quantity

6.69 Table 14 presents the estimated extent of use and financial implications to the PBS/RPBS if Yaz and Yasmin 1 x 28 tablets pack and 3 x 28 tablets pack were listed on the PBS.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated (Yaz and Yasmin 1 month pack)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of patients treated (Yaz and Yasmin 3 month pack)	█ ²	█ ²	█ ²	█ ³	█ ³	█ ³
Number of patients treated (Yaz and Yasmin total)	█ ²	█ ²	█ ²	█ ²	█ ³	█ ³
Number of scripts dispensed (Yaz 1 month pack) ^a	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Number of scripts dispensed (Yaz 3 month pack) ^b	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁶	█ ⁶
Number of scripts dispensed (Yasmin 1 month pack) ^a	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Number of scripts dispensed (Yasmin 3 month pack) ^b	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁶	█ ⁶
Number of scripts dispensed (total)	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Estimated financial implications of Yaz and Yasmin						
Cost to PBS/RPBS less copayments	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸

Source: Utilisation and cost model workbook of the submission

^a Assuming 13.04 per year as estimated by the submission.

^b Assuming 4.35 per year as estimated by the submission.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 50,000 to < 60,000

³ 40,000 to < 50,000

⁴ 10,000 to < 20,000

⁵ 100,000 to < 200,000

⁶ 90,000 to < 100,000

⁷ 200,000 to < 300,000

⁸ \$10 million to < \$20 million

- 6.70 The total cost to the PBS/RPBS of listing Yaz and Yasmin, 1 month and 3 month packs, was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$70 million to < \$80 million in the first 6 years of listing.
- 6.71 The estimated number of patients for the 1 month and 3 month products included a 50/50 patient split for Yaz and Yasmin 1 month pack, and 49.5/50.5 patient split for Yaz and Yasmin 3 month pack.
- 6.72 The estimated financial implications accounted for patients using the one product (either Yaz or Yasmin 1 month or 3 month pack) continuously for 1 year. If both the 1 x 28 tablets pack and 3 x 28 tablets pack for Yaz and Yasmin are PBS-listed, it is likely that the 1 x 28 tablets packs would only be used when initiating treatment, or for other situations where supply of a smaller quantity is indicated. The financial estimates may therefore overestimate use of the 1 x 28 tablets pack of Yaz and Yasmin, and underestimate use of the 3 x 28 tablets pack of Yaz and Yasmin.
- 6.73 The requested price for the 1 month pack of Yaz and Yasmin equates to a higher cost per tablet compared to the requested price for the 3 month pack of both products. If

the use of the 1 month packs are overestimated (and use of the 3 month packs subsequently underestimated), this would result in overestimated overall financial implications.

- 6.74 Yaz and Yasmin have a maximum quantity of 3 x 28 tablets (84 tablets), which differs from other COCs currently PBS-listed which have a maximum quantity of 4 x 28 tablets (112 tablets). If Yaz and Yasmin are PBS-listed there will be more frequent dispensings, and associated dispensing fees, and also more patient co-payments, compared to current PBS-listed COCs. The number of dispensings and associated dispensing fees, and number of co-payments, would also be higher for the 1 x 28 tablets packs of Yaz and Yasmin if PBS-listed.
- 6.75 The submission noted that patients currently taking other hormonal contraceptives listed on the PBS who may switch to Yaz or Yasmin if PBS-listed have not been accounted for in the estimates. In addition, the estimates did not account for individuals currently using other COCs not PBS-listed, including other brands of drospirenone 20 micrograms + ethinylestradiol 3 mg and drospirenone 30 micrograms + ethinylestradiol 3 mg, who may switch to using Yaz or Yasmin if they are PBS-listed. This has the potential to underestimate the usage of Yaz and Yasmin and underestimate the cost to the PBS/RPBS.
- 6.76 The submission considered the following as main sources of uncertainty in the financial estimates:
- Growth rate of the market – While there had been a decline in use of COCs, if the market stops declining the financial implications will be higher than estimated.
 - Availability of other COCs on the PBS – The submission claimed accounting for the use of other PBS-listed COCs in the financial estimates would add uncertainty to the estimates. Therefore, they have not been included in the estimated financial implications for the PBS-listing of Yaz and Yasmin products. This underestimated the financial impact, particularly if patients taking less expensive PBS-listed COCs switch to Yaz/Yasmin if PBS-listed.
- 6.77 The PSCR acknowledged the number of patients on other COCs who may switch to Yaz or Yasmin if they are PBS-listed is uncertain. However, it maintained that it expected switching to be minimal based on observed market trends for all short-acting hormone contraceptives, and that patients would likely remain on existing medicines if they are experiencing clinical benefits. The PSCR claimed that use of Yaz and Yasmin are expected to continue to decline following market trends if PBS-listed, albeit at a slower rate. To address the uncertain financial estimates, the PSCR provided a sensitivity analysis which assumed a slower decline in usage (-2%) and a slight increase with PBS-listing (2%) (Table 15). The PSCR stated this accounted for additional uptake of Yaz and Yasmin for individuals switching from other COCs to Yaz and Yasmin. The revised financial estimates estimated a total cost to the PBS/RPBS of \$70 million to < \$80 million over the first 6 years of listing (\$10 million to < \$20 million in Year 1 to \$10 million to < \$20 million in year 6). The financial estimates from this

sensitivity analysis could not be verified, and no updated Utilisation and Cost Model Workbook was provided in the PSCR, however this was provided with the pre-PBAC response.

Table 15: Financial impact of Yaz/Yasmin to the PBS/RPBS – sensitivity analysis

	2025	2026	2027	2028	2029	2030
Base case	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Sensitivity: Increased drospirenone & ethinylestradiol market growth (-2% to 2%)	\$█ ₁	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹

Source: Table 1 (p4) of PSCR

The redacted values correspond to the following ranges:

¹ \$10 million to < \$20 million

6.78 At year 6, based on the sensitivity analysis, the estimated number of patients was 50,000 to < 60,000 and the net cost to the PBS would be \$10 million to < \$20 million.

6.79 The ESC considered that there was high uncertainty as to the utilisation of Yaz and Yasmin if they were listed on the PBS.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of drospirenone with ethinylestradiol as Unrestricted benefit listings in the following forms:

- Pack containing 24 tablets 3 mg drospirenone with 20 micrograms ethinylestradiol (as betadex clathrate) and 4 inert tablets (Yaz)
- Pack containing 21 tablets 3 mg drospirenone with 30 micrograms ethinylestradiol (as betadex clathrate) and 7 inert tablets (Yasmin).

7.2 The PBAC noted the recommendation in The Senate Community Affairs Reference Committee ‘Ending the postcode lottery: Addressing barriers to sexual, maternity and reproductive healthcare in Australia’ that access to newer forms of oral contraceptive pill be available on the PBS. The PBAC also noted input provided by clinicians in the PSCR, and comments from consumers, healthcare professionals and organisations, that stated that it was beneficial to have multiple COC options available on the PBS, so that alternative COCs are available in the event that patients experience adverse effects with another COC.

7.3 The PBAC noted that the submission claimed that drospirenone offers benefits over other progestogens due to its anti-mineralocorticoid and anti-androgenic effects, and in reduced impact on weight and blood pressure. The PBAC also noted that the clinician in the sponsor hearing, as well as the consumer comments received, stated that Yaz and Yasmin provided benefits in addition to contraceptive efficacy, such as in the management of PMDD and acne. However, the PBAC considered that the evidence

- provided did not sufficiently support that Yaz and Yasmin offered any clinical advantages compared to COCs listed on the PBS.
- 7.4 The PBAC noted that the submission did not nominate a comparator, but considered that any of the COCs currently PBS-listed could be considered comparators.
 - 7.5 The PBAC noted that the submission did not provide a clinical claim, however considered that Yaz and Yasmin have similar efficacy, safety and tolerability profiles compared to other COCs.
 - 7.6 The PBAC noted that evidence presented demonstrated that Yaz and Yasmin have similar contraceptive efficacy to alternative COCs. The PBAC noted the PSCR stated that Yaz would be the only PBS-listed COC with 4 inactive tablets in a 28 day cycle, and claimed that this allows for better cycle control compared to other COCs. However, this claim was not robustly supported by the evidence provided.
 - 7.7 The PBAC noted the evidence presented on the risk of VTE with the use of COCs. The PBAC considered that the use of COCs is associated with an increased risk of VTE, and this risk has been shown to be slightly higher with COCs containing the progestogen drospirenone compared to those with levonorgestrel. However, the absolute risk of VTE in patients who use COCs is small.
 - 7.8 The PBAC noted the prices requested for Yaz and Yasmin were higher than the prices of currently PBS-listed COCs and that no economic model was presented. The PBAC noted the submission's rationale for the requested higher price, including that the requested AEMPs were slightly higher than the cost of goods. However, the PBAC considered, based on the evidence provided, that Yaz and Yasmin did not provide significant benefits in terms of greater efficacy or reduction in toxicity compared to other PBS-listed COCs to justify the higher price.
 - 7.9 The PBAC recalled that when it had previously considered submissions requesting the listing of other COCs, it had recommended listing on a cost-minimisation basis with levonorgestrel 150 micrograms with ethinylestradiol 30 micrograms combination tablets.
 - 7.10 The PBAC therefore recommended listing Yaz and Yasmin on a cost-minimisation basis to the lowest cost COC currently listed on the PBS. The PBAC advised the equi-effective doses are one tablet of Yaz/Yasmin to one tablet of levonorgestrel 150 micrograms + ethinylestradiol 30 micrograms.
 - 7.11 The PBAC noted the requested Unrestricted benefit listings of Yaz and Yasmin are consistent with the current PBS listings of other COCs. However, other PBS-listed COCs are listed as multi-month packs only, compared to the requested listings of both 1-month and 3-month packs for Yaz and Yasmin. The PBAC noted that the 1-month pack would likely only be used when patients are first initiating treatment, and the 3 month packs would be used in the majority of situations. The PBAC therefore recommended that Yaz and Yasmin be PBS-listed with a maximum quantity of 84 tablets (3 months) with 3 repeats, to provide sufficient quantity for up to

12 months of treatment.

- 7.12 The PBAC considered the financial estimates to be uncertain. The PBAC noted the overall trend in the declining use of COCs, however also noted that there was considerable interest in having additional COC options available on the PBS. Listing Yaz and Yasmin would result in a cost to the PBS due to patients switching from the private market, however it is uncertain how many additional patients will access these products once PBS listed. In light of these uncertainties, the PBAC requested a utilisation review of Yaz and Yasmin be conducted 2 years after Yaz and Yasmin are listed.
- 7.13 The PBAC advised that, under Section 101(3BA) of the *National Health Act 1953*, Yaz and Yasmin should not be treated as interchangeable with any other drugs on an individual patient basis.
- 7.14 The PBAC advised that Yaz and Yasmin are suitable for prescribing by nurse practitioners.
- 7.15 The PBAC recommended that the Early Supply Rule should not apply.
- 7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Yaz and Yasmin are not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over other COCs currently PBS listed, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DROSPIRENONE WITH ETHINYLESTRADIOL					
drospirenone 3 mg + ethinylestradiol 20 microgram tablet [24] (& inert substance tablet [4], 28	NEW	3	3	3	Yaz
drospirenone 3 mg + ethinylestradiol 20 microgram tablet [24] (& inert substance tablet [4], 3 x 28	NEW	1	3	3	Yaz
drospirenone 3 mg + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 28	NEW	3	3	3	Yasmin
drospirenone 3 mg + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 3 x 28	NEW	1	3	3	Yasmin
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners				
	Restriction type: <input checked="" type="checkbox"/> Unrestricted benefit				

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Yaz and Yasmin are established off-patent products which are currently privately available to Australian women. Bayer made submission to the PBAC in response to stakeholder interest in providing women with more contraceptive choice through the Pharmaceutical Benefits Scheme (PBS). We are reviewing the PBAC outcomes to determine next steps.

Bayer is committed to advancing women's health by providing solutions for her different reproductive needs and advocating for equitable access.

Addendum to the July 2024 PBAC Public Summary Document:

**14.08 DROSPIRENONE WITH ETHINYLESTRADIOL,
Pack containing 24 tablets 3 mg drospirenone with
20 micrograms ethinylestradiol (as betadex
clathrate) and 4 inert tablets,
Pack containing 21 tablets 3 mg drospirenone with
30 micrograms ethinylestradiol (as betadex
clathrate) and 7 inert tablets,
Yaz[®], Yasmin[®],
Bayer Australia Ltd.**

11 Background

- 11.1 On 10 October 2024, in response to a request from the Minister, the PBAC convened a stakeholder meeting to increase understanding of what evidence is available that may demonstrate that newer oral contraceptive pills (OCP) offer additional benefits compared to older generation oral contraceptives.
- 11.2 Key points from the stakeholder meeting discussion included:
- Non-adherence to hormonal contraceptives due to cost increases the risk of unintended pregnancy, and there are individual and societal costs when contraceptives are not affordable for individuals.
 - Many women will require contraception throughout their life until menopause, and their circumstances (e.g. risk factors, lifestyle needs) and requirements will change. Individuals may require different contraceptives at different times in their life, and clinicians highlighted the importance of finding an OCP that was most suitable for the person and their lifestyle. In addition, not every individual responds the same way to OCPs, and it is highly individualised as to which contraceptive medicines people may or may not tolerate.
 - Through the life course, individuals often trial different OCPs as their needs and circumstances changed. Stakeholders noted that, when individuals commence OCPs, they will often try a product that is PBS-listed first, even though a non-PBS listed OCP could be a better choice.
 - Stakeholders noted having a range of contraceptive options is important in providing choices for individuals in finding the most appropriate contraceptive medicine for them at various points in their life. This includes non-oral options, such as the etonogestrel/ethinylestradiol vaginal ring.

Public Summary Document – July 2024 PBAC Meeting with November 2024 Addendum

- Stakeholders raised that it was important for the newer currently non-PBS contraceptives to be available as additional treatment choices.
 - Clinicians noted that conditions like polycystic ovarian syndrome and premenstrual dysphoric disorder respond better to new OCPs because they have better anti-androgenic effects.
 - The Stakeholder discussed the option of restricting the use of newer OCP to second line treatment. The participants highlighted the downsides of such an approach as access to the right medicine would be needlessly delayed on a short or even longer term basis.
 - Representatives from pharmaceutical companies raised that certain contraceptives have higher manufacturing costs due to their form or raw ingredients, and that manufacturing costs are higher than when current PBS-listed oral contraceptives were first listed.
- 11.3 Following the outcomes of the stakeholder meeting, Bayer Australia Limited (Bayer) wrote to the PBAC requesting reconsideration of its July 2024 recommendation to list Yaz and Yasmin on cost-minimisation basis to the lowest cost combined oral contraceptive (COC) pill currently listed on the PBS.
- 11.4 In its letter, Bayer reiterated that the requested DPMQs (\$█ (1 x 28 tablet pack) and \$█ (3 x 28 tablet pack)) were lower or consistent with the prices currently paid for private prescriptions for these products in Australia and the AEMPs requested (\$█ and \$█, respectively) were lower than the prices offered to similar markets overseas.
- 11.5 The Department provided a sensitivity analysis of the estimated net financial implications of listing PBS for Yaz and Yasmin, using the proposed pricing and a varied DPMQ range guided by private pricing of generic brands of drospirenone with ethinylestradiol (Table 16). Sensitivity analyses were calculated using the July 2024 submission financial model.

Table 16: Sensitivity Analysis of estimated net financial impact to the PBS/RPBS for drospirenone 3 mg & ethinylestradiol 20 microgram (Yaz) and drospirenone 3 mg & ethinylestradiol 30 microgram (Yasmin)

Estimated net financial impact to the PBS/RPBS Yaz/Yasmin (AEMP, DPMQ)	2025	2026	2027	2028	2029	2030
Sponsor proposed Yaz and Yasmin 3 month pack (\$█, \$█) Yaz and Yasmin 1 month pack (\$█, \$█)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Sponsor proposed sensitivity: Increased drospirenone & ethinylestradiol market growth (-2% to 2%)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Yaz and Yasmin 3 month pack (\$█, \$█) Yaz and Yasmin 1 month pack (\$█*, \$█)	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ²
Sensitivity : Increased drospirenone & ethinylestradiol market growth (-2% to 2%)	█ ¹	█ ¹	█ ²	█ ¹	█ ¹	█ ¹
Yaz and Yasmin 3 month pack (\$█, \$█) Yaz and Yasmin 1 month pack (\$█*, \$█)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Sensitivity: Increased drospirenone & ethinylestradiol market growth (-2% to 2%)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²

*the AEMP for the 1 month pack was calculated during the evaluation as a proportion of the AEMP of 3 month pack.

The redacted values correspond to the following ranges:

1 \$10 million to < \$20 million

2 \$0 to < \$10 million

11.6 The Department provided a summary of the DPMQs for OCPs currently listed on the PBS and an overview of the distribution of the cost per prescription of Yaz and Yasmin based on the 2023 utilisation of PBS listed OCPs (Table 17).

Table 17: Distribution of cost per prescription of Yaz/Yasmin by patient category

	Percentage of prescriptions*	Yaz/Yasmin 3 month pack – cost to patient per prescription	Yaz/Yasmin 3 month pack – cost to Government per prescription	Yaz/Yasmin -1 month pack – cost to patient per prescription	Yaz/Yasmin -1 month pack – cost to Government per prescription
General	82.12 %	\$31.60	\$30.25	\$29.35	0
General – safety net	0.08%	\$7.70	\$54.15	\$7.70	\$21.65
Concession	16.66%	\$7.70	\$54.15	\$7.70	\$21.65
Concession- safety net	1.09%	0	\$61.85	0	\$29.35

* based on 2023 data for existing PBS listed hormonal oral contraceptives. RPBS data is not displayed. The patient co- payments used are for 2024. The cost to Government calculated using a DPMQ of \$█

12 PBAC Outcome

12.1 The PBAC provided further advice regarding its July 2024 recommendation to list drospirenone with ethinylestradiol as Unrestricted benefit listings in the following forms:

- Pack containing 24 tablets 3 mg drospirenone with 20 micrograms ethinylestradiol (as betadex clathrate) and 4 inert tablets
- Pack containing 21 tablets 3 mg drospirenone with 30 micrograms ethinylestradiol (as betadex clathrate) and 7 inert tablets.

12.2 The PBAC noted the recommendation from the Senate Community Affairs Reference Committee ‘Ending the postcode lottery: Addressing barriers to sexual, maternity and reproductive healthcare in Australia’ that access to newer forms of oral contraceptive

pill be available on the PBS.

- 12.3 The PBAC recalled its July 2024 recommendation to list Yaz and Yasmin on a cost-minimisation basis to the lowest cost COC currently listed on the PBS. The PBAC recalled that the submission considered in July 2024 claimed that Yaz and Yasmin provided clinical benefits in addition to contraception compared to other COCs, however at that time the PBAC considered that there was a lack of evidence provided to demonstrate these additional benefits compared to other COC options.
- 12.4 The PBAC noted the outcomes of October 2024 stakeholder meeting, including:
- the importance of the availability of various subsidised hormonal contraceptive options, so that cost is not a barrier to accessing the most appropriate option, which may vary at different points in life.
 - newer oral contraceptives are more appropriate in particular clinical situations.
- 12.5 The PBAC noted the requested AEMPs for Yaz and Yasmin were slightly higher than the cost of goods.
- 12.6 The PBAC noted the current DPMQs for OCPs listed on the PBS, along with the private market pricing of newer oral contraceptives. The PBAC recalled its recommendations for the COCs on the PBS were made before cost-effectiveness analysis was required.
- 12.7 The PBAC considered drospirenone with ethinylestradiol may provide a different option for some patients than the currently PBS-listed COCs and that it was important to have a range of COC options on the PBS. The PBAC considered that drospirenone with ethinylestradiol offers benefits in certain clinical situations compared with other COCs listed on PBS. The PBAC therefore considered that the prices proposed by the sponsor were acceptable.

Outcome:

Recommended

13 Recommended listing

13.1 Add new item

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
DROSPIRENONE WITH ETHINYLESTRADIOL					
drospirenone 3 mg + ethinylestradiol 20 microgram tablet [24] (& inert substance tablet [4], 28	NEW	3	3	3	Yaz
drospirenone 3 mg + ethinylestradiol 20 microgram tablet [24] (& inert substance tablet [4], 3 x 28	NEW	1	3	3	Yaz
drospirenone 3 mg + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 28	NEW	3	3	3	Yasmin
drospirenone 3 mg + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 3 x 28	NEW	1	3	3	Yasmin

Restriction Summary / Treatment of Concept:	
	Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction type: <input checked="" type="checkbox"/> Unrestricted benefit

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

14 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

15 Sponsor’s Comment

Bayer welcomes the PBAC’s reconsideration of its July 2024 cost-minimisation recommendation for YAZ and YASMIN (drospirenone and ethinylestradiol). Bayer wishes to acknowledge the multi-stakeholder collaboration in successfully finding a sustainable pathway for a PBS listing for YAZ and YASMIN. Bayer remains committed to advancing women’s health by providing solutions for her different reproductive needs and advocating for equitable access.