

## NEW MEDICINES ON THE MARKET

### Evaluated information for the NHS

## YASMIN®

### Summary

- Yasmin® (ethinylestradiol 30mcg / drospirenone 3mg) is a combined oral contraceptive.
- It has similar contraceptive efficacy and cycle control to other combined oral contraceptives. Contrary to initial claims by the manufacturer, there is no compelling evidence that its effects on skin, premenstrual symptoms, and feelings of well being are any different to standard combined oral contraceptives. A clinically important effect on weight gain has not been demonstrated.
- Yasmin® is generally well tolerated. The frequency and type of adverse event reported in clinical trials are typical of those observed with other combined oral contraceptives.
- The risk of venous thromboembolic events (VTE) and arterial disease with Yasmin® cannot be quantified from current evidence and is unknown.
- Yasmin® costs significantly more than other combined oral contraceptives. It offers no proven advantages to warrant the increased cost.

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Region of Origin to whom queries should be directed: Newcastle

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## YASMIN®

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<b>Approved Name:</b>	Ethinylestradiol and drospirenone
<b>Brand Name (Manufacturer):</b>	Yasmin® (Schering Health)
<b>Presentation:</b>	Oral tablet containing ethinylestradiol 30 mcg and drospirenone 3 mg.
<b>BNF Therapeutic Class:</b>	Combined oral contraceptive (BNF 7.3.1)
<b>Licensed Indications:</b>	Oral contraception.
<b>Dosage and Administration:</b>	One tablet daily for 21 days; subsequent courses repeated after 7-day tablet free interval (during which withdrawal bleeding occurs)
<b>Sector of Use:</b>	Hospital [Y ] Primary Care [Y]

<b>Therapeutic Comment:</b>	Yasmin® has similar contraceptive efficacy and cycle control to other combined oral contraceptives. It offers no proven advantages to warrant the increased cost.
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<b>Cost and Course Details:</b>	Cost for 3 x 21 days	£14.70
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<b>Treatment Alternatives:</b>		Cost for 3 x 21 days
	Marvelon®	£6.70
	Femodene®	£6.84
	Ovranette®	£2.46
	Microgynon 30 ED®	£2.56
	Microgynon 30®	86p
	(From MIMS March 2003)	

## INTRODUCTION

Approaches to developing new oral contraceptives include reducing the dose of oestrogen and progestogen used and using progestogens with a more favourable pharmacological profile.<sup>1</sup> Most combined oral contraceptives contain ethinylestradiol in combination with progestogens derived from the 19-nortestosterone i.e. levonorgestrel, norethisterone, desogestrel or gestodene. At doses commonly used in oral contraceptives these progestogens do not have the anti-mineralocorticoid activity of natural progesterone, which compensates for the oestrogen-induced salt and water retention.<sup>1</sup> The ideal progestogen would have the antiminerlocorticoid activity similar to that of natural progesterone.<sup>2</sup>

## PHARMACOLOGY

Yasmin® contains ethinylestradiol and the progestogen drospirenone. Drospirenone is derived from 17  $\alpha$ -spiro lactone and is an analogue of the aldosterone antagonist, spironolactone. Its pharmacological properties are similar to those of natural progesterone. The contraceptive effect of Yasmin® is based on the interaction of various factors, including the inhibition of ovulation and the changes in the endometrium.<sup>3</sup>

## PHARMACOKINETICS

**Ethinylestradiol:** Ethinylestradiol is absorbed within two hours of oral administration of Yasmin® (absorption is slowed by food). It is rapidly metabolised, primarily by conjugation and aromatic hydroxylation via the hepatic cytochrome P450 (CYP) 3A4 isoenzyme, and is excreted in urine and faeces.<sup>4</sup>

**Drospirenone:** Drospirenone is absorbed within two hours of oral administration of Yasmin® (absorption is slowed by food). Serum drospirenone concentrations were increased in women with moderate renal impairment. Prior to elimination (which is both faecal and renal), drospirenone is extensively metabolised in the liver, the two main metabolites found in the plasma are pharmacologically inactive.<sup>4</sup>

## EFFICACY

There are two open label comparative studies with Marvelon®, a formulation that contains the same oestrogen combined with desogestrel, a third-generation progestogen (see Table 1). In the first study lasting for 26 cycles (n=887) there were three pregnancies in each group and all were thought to be due to user rather than method failure.<sup>2</sup> In the second study 2069 women were randomised in a ratio of 4:1 to either Yasmin® or Marvelon® for 13 cycles.<sup>1</sup> There were 10 pregnancies in the Yasmin® group compared with one in the Marvelon® group. No level of statistical difference is given. Of these 11 pregnancies only one, in the Yasmin® group, was considered by the authors to be due to method failure. When corrected for other factors (missed tablets, diarrhoea, etc) the number of pregnancies per 100 women-years use was 0.07 with Yasmin® and 0.28 with Marvelon®.<sup>1</sup> This is reported to be similar to other oral contraceptives.<sup>4</sup>

The frequency and pattern of intermenstrual bleeding, withdrawal bleeding, amenorrhoea and premenstrual symptoms were similar in recipients of Marvelon® and Yasmin® in both studies.

## Weight

In the 13 cycle study mean weight loss during treatment was statistically significantly greater with Yasmin® than with Marvelon® although the difference was very small (0.46 kg vs. 0.19 kg  $p < 0.0072$ ).<sup>1</sup> In the 26 cycle study the authors report a significant difference between the two groups although no actual figures are presented.<sup>2</sup> The results from both studies included all women who received some treatment, including those who dropped out of the study due to weight gain. In both studies most women maintained a stable body weight (+/- 2 kg).<sup>1,2</sup>

In both studies women measured their own weight at home and knew which preparation they were taking.

In a small (n=80) double blind study a significant but small difference on weight was observed after 6 cycles between women taking Microgynon 30® (levonorgestrel 150 mcg, ethinylestradiol 30 mcg) compared with Yasmin® (+ 0.68 kg vs - 0.78 kg).<sup>5</sup>

## Skin

In the 13 cycle study the incidence and severity of acne was reduced in both groups from 21.5% to 7.8% in the Yasmin® group and from 20.1% to 8.2% in the Marvelon® group.<sup>1</sup>

In a double blind randomised comparative study over 9 cycles in 128 women with mild to moderate acne, the median total acne lesion count decreased to a similar extent in women receiving Yasmin® 62.5% and those receiving Dianette® 58.8% (cyproterone 2 mg and ethinylestradiol 35 mcg).<sup>6</sup>

In November 2002, Schering withdrew its promotional material for Yasmin® following a request from the MCA.<sup>7</sup> This followed an article that appeared in the

Drug and Therapeutics Bulletin in August 2002, which argued that there was no compelling published evidence that Yasmin® offered any advantages over other, longer established combined oral contraceptives with regards to weight gain, skin condition or premenstrual symptoms.<sup>8</sup>

## ADVERSE EFFECTS

Discontinuation rates were similar between groups and were around 20%<sup>1</sup> and 30%<sup>2</sup> for each of the two efficacy studies. 9% of women withdrew due to adverse events, most frequently headache, menstrual disorders, nausea / vomiting and weight gain.<sup>1</sup>

There have been reports of venous thromboembolism among women taking Yasmin®.<sup>9</sup> The absolute risk of thromboembolism in users of combined oral contraceptives is very low (15/100,000 or 25/100,000 for second and third generation respectively). This is considerably less than the risk during pregnancy (60/100,000). No thrombotic events were reported back from comparative trials.<sup>1,2</sup> Yasmin® has been on the European market since November 2000 giving an estimated 2 million women-years of use. The observational reporting rate of VTE is currently 6.5/100,000 women years of use. These are spontaneous reports and the likelihood of under reporting should be considered.<sup>10</sup>

## CONTRAINDICATIONS AND PRECAUTIONS (see SPC)

The SPC gives a comprehensive list of conditions when combined oral contraceptives should not be used and where there are special precautions for use.

## REFERENCES

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**Table 1 – Comparative studies of two oral contraceptives containing either drospirenone or desogestrel.**

Ref No	Design of Study	Treatments Assessed	Primary Outcome Measures	Results and Comments		
				Assessment	Yasmin®	Marvelon®
1.	Multi-centre, randomised, open-label	Yasmin® (n=1657) and Marvelon® (n=412) for 13 cycles, follow up for 6 weeks. Both preparations were taken orally for 21 consecutive days, followed by a tablet free interval of 7 days.	Contraceptive efficacy (analysed using the Pearl index), cycle control, skin condition, blood pressure and body weight and adverse events	Assessment	Yasmin®	Marvelon®
				Pearl index♦	0.07	0.28
				Cycle control	No significant differences – good with low incidence of intermenstrual bleeding	
				Acne	Reduced from 21.5% to 7.8%	Reduced from 20.1% to 8.2%
				Seborrhoea	Reduced from 11.7% to 2.8%	Reduced from 11.9% to 2.5%
				Physical findings	Mean systolic and diastolic pressure slightly lower than baseline but not significant	
				Body weight	Mean weight loss 0.46kg (1lb)	Mean weight loss 0.19kg (0.4lbs)
				Adverse events	38.5%	32.3%
				Typical of those associated with an oral contraceptive		
2.	Multi-centre, randomised, open-label	Yasmin® (n=442) and Marvelon® (n=445) for 26 months, follow up for 3 months. Both preparations were taken orally for 21 consecutive days, followed by a tablet free interval of 7 days.	Contraceptive efficacy (analysed using the Pearl index), cycle control, blood pressure and body weight and adverse events	Assessment	Yasmin®	Marvelon®
				Pearl Index	0.41	0.41
				Cycle control	No significant differences – good with low incidence of intermenstrual bleeding	
				Physical findings	A statistical difference between the two groups, although no actual figures are presented.	
				Premenstrual syndrome	No significant difference	
				Blood pressure	Mean systolic and diastolic pressure slightly lower than baseline but not significant	
				Adverse events	42.5%	42.0%

♦Pearl index = The number of pregnancies per 100 woman years. (If out of 100 women using a contraceptive over a period of one year, one woman becomes pregnant the Pearl index is 1.0.)