Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Drospirenone and Ethinyloestradiol

Proprietary Product Name: YAZFlex

Sponsor: Bayer Australia Pty

October 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright
© Commonwealth of Australia 2014
This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	adverse event
AUC	area under curve
CER	clinical evaluation report
Cmax	maximum concentration achieved
CMI	consumer medicine information
COC	combined oral contraceptive
DRSP	drospirenone
EE	ethinyloestradiol
EU	European Union
EURAS	European Active Surveillance Study
FSH	follicle stimulating hormone
LH	luteinising hormone
LLOQ	lower limit of quantification
OC	oral contraceptive
PI	product information
PK	pharmacokinetic
PMDD	premenstrual dysphoric disorder
PMS	premenstrual syndrome
PPK	population pharmacokinetics
RMP	risk management plan
SAE	serious adverse event
TGA	Therapeutic Goods Administration
TVU	transvaginal ultrasound
VTE	venous thromboembolism

I. Introduction to product submission

Submission details

Type of Submission	Change in dosage regimen
Decision:	Approved and Withdrawn in part[1]
Date of Decision:	28 February 2012
Active ingredient(s):	Drospirenone and ethinyloestradiol (as betadex clathrate)
Product Name(s):	YAZFlex
Sponsor's Name and Address:	Bayer Australia Ltd 875 Pacific Hwy Pymble 2073 NSW
Dose form(s):	Tablet
Strength(s):	3 mg (drospirenone) and 20 µg (ethinyloestradiol)
Container(s):	Plastic cartridges (within oPA/Al/PE blisters)
Pack size(s):	1 x 30 tablets, 4 x 30 tablets and 1 x 30 tablets plus dispenser
Approved Therapeutic use:	*YAZFlex is indicated for use as:* *1. an oral contraceptive* *2. treatment of moderate acne vulgaris in women who seek oral contraception.*
Route(s) of administration:	Oral (PO)
Dosage:	One tablet to be taken daily at about the same time with some liquid. Tablet taking is continuous for at least 24 consecutive days. See also Product Information (PI).
ARTG Number (s)	179878

Product background

In February 2008 the sponsor Bayer Australia Ltd registered a composite pack of 24 fixed combination tablets containing drospirenone (DRSP) 3 mg and ethinyloestradiol (EE) 0.02 mg (as betadex clathrate) and 4 placebo tablets under the trade name 'YAZ'. The combination of ethinyloestradiol and drospirenone has also previously been approved for use as Yasmin tablets (0.03 mg ethinyloestradiol and 3 mg drospirenone). It is also present in the hormone replacement therapy product Angeliq 1/2.

[1] On 27 February 2012 Bayer withdrew the indication '*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 3 months. YAZ has not been evaluated for treatment of PMS (premenstrual syndrome), See CLINICAL TRIALS*' from this YAZ Flex application.

YAZFlex and YAZ are low dose formulations of Yasmin in which the reduced amount of ethinyloestradiol is complexed with β-cyclodextrin (1:2) as ethinyloestradiol betadex clathrate to ensure shelf stability at low concentrations.

This AusPAR describes the application by Bayer Australia Ltd to register a change in dosage regimen (and a new presentation pack) for ethinyloestradiol ± drospirenone fixed-combination tablets. The maximum duration of the consecutive intake phase for the active ingredients is proposed to be increased from 24 days (current product, YAZ) to up to 120 days (proposed product, YAZFlex).

The sponsor states that YAZFlex has been developed to provide women with the flexibility to manage the length of their menstrual cycle according to their individual needs.

During Days 25 to 120 a woman may decide when to take a 4 day tablet free interval. This 4 day tablet free interval has to be taken no later than after 120 days of continuous tablet intake and should not be longer than 4 days. After each 4 day tablet free interval, a new intake cycle of a minimum of 24 days to a maximum of 120 days starts.

The sponsor will market YAZFlex in an innovative tablet dispenser which has a reminder function. This dispensing device combines a mechanical tablet dispenser and an electronic counting system with a graphical user interface. A cartridge containing 30 YAZFlex tablets is to be inserted in the dispenser by the woman prior to use and replaced with a new cartridge once all tablets have been released. The user interface guides the woman through the intake regimen. The display shows when a tablet has to be taken. The woman can also obtain information about the day of the current treatment cycle, the number of tablets remaining in the cartridge and whether she may take the 4 day tablet free interval. In addition, it indicates to the woman if tablets are missed and extra, nonhormonal contraceptive methods should be used. During the hormone free interval, no placebo tablets are provided. The dispensing device will display the day of the break and after 4 days start a new intake cycle and remind the woman to take her tablet when the reference intake time is reached. The dispensing of each tablet is a mechanical function actuated by the user. The function of the electronic component of the device is only to give appropriate prompts to the user and to record the dispensing of the tablets.

The sponsor proposed an identical indication for YAZFlex to that of YAZ in the application letter, that is;

- *Oral contraception.*
- *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 assesses beyond three cycles. YAZ has not been evaluated for treatment of PMS (premenstrual syndrome), See CLINICAL TRIALS.1*

Regulatory status

In April 2012 the European medicines Agency (EMA)/ The Committee for Medicinal Products for Human Use, formerly known as Committee for Proprietary Medicinal Products(CHMP) concluded that the benefits of YAZFlex outweigh its risks, and thus, marketing authorisation could be granted in all European Union (EU) Member States as well as Iceland and Norway.

YAZFlex was approved in Switzerland on 26 July 2013 under the tradename Flexyess.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Introduction

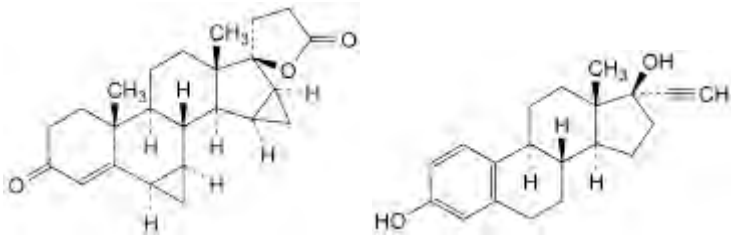
The electronic dispenser allows for patients to periodically take a 4 day break from dosing, hence no placebo tablets are included. The electronic dispenser is to be listed separately on the Australian Register of Therapeutic Goods (ARTG) as a device.

There are recently published European Pharmacopeia (EP)/British Pharmacopeia (BP) 2011 and US Pharmacopeia (USP) 34 monographs for drospirenone but no compendial monographs for finished products containing drospirenone. There are BP/USP monographs for ethinyloestradiol and BP/USP monographs for a number of ethinyloestradiol-containing tablets.

Drug substance (active ingredient)

Drospirenone is a synthetic progestogen. Ethinyloestradiol is a synthetic derivative of oestradiol, a naturally occurring oestrogen. Their structures are shown in Figure 1.

Figure 1. Chemical structures of active ingredients.



Drospirenone **Ethinyloestradiol**

As per the registered 'YAZ' product, the ethinyloestradiol drug substance is pre-formulated with betadex (betacyclodextrin) prior to tablet manufacture to form an inclusion complex (or clathrate). This is claimed to enhance the *in vitro* stability of the ethinyloestradiol without affecting the *in vivo* bioavailability. There are BP and USP monographs for the cyclodextrin betadex.

The drug substances are manufactured by Bayer Pharma AG, Germany.

A number of minor changes have been made to aspects relating to the drug substance drospirenone. The proposed drospirenone specification has also been revised in line with the EP/BP Monograph for drospirenone.

Minor changes have been made to the ethinyloestradiol specification; other aspects relating to the ethinyloestradiol drug substance are substantially unchanged. The changes to the specification follow revision of the ethinyloestradiol European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability (CEP), which in turn follows amendment to the applicable EP monograph.

The free betadex used in the clathrate is the subject of a CEP; previously this was not the case. The CEP has expired; however, the company notes that a new CEP was expected by the end of 2011. This issue will need to be addressed prior to a decision on registration.

Drug product

The tablets are to be manufactured by Bayer Pharma AG, Germany (as per the registered product). The manufacturing process and finished product specifications are unchanged.

Packaging and stability

The tablets are to be packed into a dispenser which is then packed into a hermetically sealed blister.

Two blister platforms are proposed. Both are polyamide/aluminium/polyethylene (oPA/Al/PE) blisters with the PE layer on the inside. The two platforms have different adhesives and different thicknesses of PE (30 or 40 μm).

The materials are acceptable for use in the product.

Under accelerated storage conditions a decline in ethinyloestradiol assay was observed in the stability batches. The submitted data were otherwise acceptable.

Adequate in-use and photostability data were provided.

A shelf-life of 18 months when stored below 30 C° in the proposed packaging is recommended.

Labelling of the device

The device has been evaluated by the Office of Laboratories and Scientific Services at TGA with regard to its usability and the quality of its instructions for use.

At first glance, the device seemed to be overly complicated and cryptic. However, the instructions for use were found to provide clear concise instructions making ample use of illustrations to eliminate all possibility of ambiguity. There were no objections to the approval of the submission on the basis of device design and usability.

However, during examination it was found that the device can eject its entire contents (up to 30 tablets) at one sitting within a short time. It was therefore recommended that the applicant add a 'Keep Out of the Reach of Children' warning to the device itself (this warning already appears on the Instructions Manual).

This recommendation was put to the sponsor. The sponsor did not believe it is necessary to add the warning statement. The sponsor noted that a similar concern was raised by the Netherlands Health Authority as part of the ongoing European submission and has provided the response given to the Netherlands Health Authority for consideration by TGA. Clinical comment on this issue was sought.

Quality summary and conclusions

Subject to satisfactory resolution of the issues detailed above, there were no objections to the registration of YAZFlex ethinyloestradiol (as betadex clathrate) 20 μg and drospirenone 3 mg tablet dispenser pack with regard to chemistry, manufacturing and controls.

III. Nonclinical findings

Introduction

The nonclinical part of the current Australian submission comprised 59 studies. These were claimed to represent nonclinical studies not previously evaluated by the TGA. The

thoroughness of the sponsor's identification of previously evaluated data was questioned prior to and at submission and a revised Nonclinical Table of Contents listing 29 unevaluated studies was ultimately provided. Upon evaluation, the actual number of new studies has been determined to be 23. None of these were of direct relevance to the effect of the modified dosing regimen on efficacy or safety.

Pharmacology

Two new studies were submitted. The data add to the already well established pharmacological characterisation of the two active ingredients. In the first study, ethinyloestradiol was shown to possess high affinity for the oestrogen receptor (rat and human uterus), moderate progesterone receptor affinity (rabbit and human uterus), no affinity for the androgen receptor (rat prostate), low affinity for the glucocorticoid receptor (rat thymus), little affinity for human sex hormone binding globulin (SHBG) and no affinity for human cortisol binding globulin (CBG). In the second study, the progestogenic activity of drospirenone was again demonstrated in vivo in a study in rats, with a preferential action on the uterus compared to mammary gland evident.

Pharmacokinetics

Co-administration of ethinyloestradiol had no significant effect on exposure to drospirenone in a single dose study in monkeys. This is consistent with the reported lack of effect of ethinyloestradiol on the pharmacokinetics of drospirenone in clinical studies. New distribution and excretion studies in rats demonstrated no persisting tissue specific retention of radioactively labelled (^{3}H)-ethinyloestradiol-derived radioactivity and significant biliary excretion of both ^{3}H-ethinyloestradiol and ^{3}H-drospirenone derived radioactivity. These aspects of the pharmacokinetic profile were known from previously evaluated data. Toxicokinetic data submitted in support of a previously evaluated peri-/postnatal development study in rats with ethinyloestradiol and drospirenone in combination are not of utility in assessing relative exposure due to the limited sampling regimen used (one or two time points per day; area under plasma concentration time curve (AUC) not calculable).

Toxicology

All new safety related studies were Good Laboratory Practice (GLP) compliant.

Acute toxicity

A single-dose toxicity study with ethinyloestradiol and drospirenone in combination (1:100 ratio) in rats indicated a low order of acute toxicity by the oral route (maximum non-lethal dose, 2000 mg/kg). This is consistent with previously evaluated studies for the single agents. Given the existing data, such a study with the combination is not required according to the relevant TGA adopted EU guideline[2].

Repeat-dose toxicity and carcinogenicity

No new data on repeat dose toxicity or carcinogenicity were submitted. Studies evaluated for the original application to register ethinyloestradiol ± drospirenone involved continuous once daily dosing and so are relevant to support the modified dosing regimen

[2] Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products. EMEA/CHMP/SWP/258498/2005. <http://www.tga.gov.au/pdf/euguide/swp25849805final.pdf>

for YAZFlex. A new mechanistic study revealed that ethinyloestradiol was negative in the rat liver foci bioassay.

Reproductive toxicity

The sponsor has submitted a set of new embryofetal development studies in rats conducted with ethinyloestradiol and drospirenone in combination (1:100 ratio; oral (PO) administration). Embryofetal development studies in rats and rabbits submitted for the original registration of Yasmin were conducted with drospirenone alone; similar studies with ethinyloestradiol alone had already been evaluated. This approach is acceptable to support a fixed-combination product[2]. Of note, there was a previously evaluated study with the combination in rats that examined the potential for feminisation of fetuses but the treatment period was not for the full period of organogenesis and the fetal examination was more limited than expected for a proper embryofetal development study.

Relative exposure

Exposure ratios for drospirenone achieved in the definitive embryofetal development study with the combination have been calculated based on animal: human plasma area under AUC from time zero to 24 h ($AUC_{0-24\,h}$) (see table below). AUC values were not calculable for ethinyloestradiol in the study as plasma levels were most often below the limit of quantification (50 pg/mL).

Table 2. Relative exposure

Species	Study	Dose (mg/kg/day); PO [ethinyloestradiol/ drospirenone]	Drospirenone $AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio#
Rat (SD)	A20498	0.01 / 1	124	0.16
		0.03 / 3	350	0.5
		0.1 / 10	2400	3
Human (Caucasian women)	A03328	[20 µg / 3 mg]	763	–

= animal: human plasma $AUC_{0-24\,h}$; AUC values for animals are the mean of values obtained on GD6 and GD17. SD=standard deviation.

The newly submitted definitive study with the combination revealed embryolethality (increased post implantation loss) but no teratogenicity at the highest dose in rats (0.1/10 mg/kg/day ethinyloestradiol/drospirenone orally (PO)) and an increased incidence of skeletal variations (principally wavy ribs) and retardation of ossification at ≥0.03/3 mg/kg/day. These adverse effects on embryofetal development were observed at doses yielding exposure levels of ethinyloestradiol and drospirenone below or only low multiples of the clinical exposure. YAZFlex is to be contraindicated in known or suspected pregnancy (as YAZ is).

Impurities

Impurity limits for YAZFlex have been tightened in some respects for the drug substances and are unchanged for the drug product compared to YAZ. Toxicological acceptability was established previously.

Additional genotoxicity studies with crude or spiked batches of ethinyloestradiol containing impurities named in the specifications were submitted. There were some positive findings in in vitro assays for clastogenicity (generally in the presence of metabolic activation) but negative results were obtained in assays for bacterial mutagenicity and for unscheduled deoxyribonucleic acid (DNA) synthesis (rat liver) and clastogenicity (mouse micronucleus test) in vivo. At the proposed limits, patients would receive a maximum of 0.5 µg named impurities per day. This is well below the threshold of toxicological concern (TTC) value of 1.5 µg/day. Furthermore, on a body surface area basis, the doses of the individual impurities that were negative in the *in vivo* test for clastogenicity were >800000 times the maximum potential human dose. Accordingly, the impurities are not considered to pose a risk to patient safety.

Nonclinical summary and conclusions

- The nonclinical part of the current submission contained previously unevaluated data on pharmacology, pharmacokinetics, single dose toxicity, embryofetal development, induction of liver foci and on the genotoxicity of impurities.
- None of the new data were of specific relevance to the modified dosing regimen. Previously evaluated toxicity studies submitted in the original application to register the combination involved continuous once daily administration. Hence, the nonclinical assessment made for the original application for registration is able to support this application.
- New data evaluated in this report do not reveal new hazards or alter conclusions regarding the pharmacological, pharmacokinetic or toxicological profiles of ethinyloestradiol or drospirenone drawn previously.
- There are no nonclinical objections to the registration of YAZFlex provided that the draft Product Information document is amended as directed. Specifically, information on the genotoxicity of ethinyloestradiol must be added.

IV. Clinical findings

Introduction

YAZFlex is one of a portfolio of three products being developed by the sponsor which are variations of the extended cycle principle. The others are YAZ Extend, in which the 120 day active cycle is taken without interruption, irrespective of the occurrence of (unintended) bleeding episodes; and YAZ Stop&Go, in which the user can schedule the 4 day tablet free intervals to occur at any time from 24 up to 120 days from the start of the cycle, irrespective of episodes of spotting or bleeding, so as to schedule withdrawal bleeding episodes according to convenience. These latter two products are not proposed for marketing in Australia at this time but are used as comparators in the Phase III efficacy studies reviewed in this report.

There is some conflicting information about the question of user initiated tablet free intervals. Despite the above definitions taken from the sponsor's Clinical Overview, it is stated in the product development rationale on the following page of that document, and in the draft product information (PI), that women using YAZFlex may choose to initiate a

tablet free period at any time from Day 25 onwards of a 120 day active tablet cycle, making 'managed bleeding' a feature of both YAZFlex and YAZ Stop&Go; however, the penultimate paragraph in the sponsor's Clinical Overview defines the Stop&Go regimen as differing from YAZFlex only in the provision for these episodes and then the following paragraph states that YAZFlex;

> *'will give women the option to extend the length of their menstrual cycle according to their individual needs or based upon the occurrence of bleeding episodes'.*

The term 'YAZFlex' of course indicates flexibility and this is doubtless how it will be interpreted by users.

The requested indications for YAZFlex are identical to those of YAZ. The task of this evaluation, therefore, will be to determine whether efficacy and/or safety of the product are altered in respect of any of the above indications either as a result of the longer period of continuous administration of the active tablets or as a result of the use of the dispensing device insofar as it might affect compliance.

The Australian application is identical to those submitted through the decentralised European procedure except for the inclusion of clinical study reports provided previously to TGA for the evaluation of related products YAZ, Yasmin and Angeliq 1/2.

Good Clinical Practice (GCP) aspects

The four clinical studies submitted for evaluation describe appropriate procedures for ethical study conduct including giving of information and consent arrangements, counselling, and clinical care when appropriate, consistent with relevant international guidelines. The documentation of these procedures is consistent between the various studies and overall compliance with Good Clinical Practice (GCP) appears satisfactory.

Pharmacokinetics

Introduction

Pharmacokinetic (PK) data were collected in the course of pivotal efficacy Study A40196. A population pharmacokinetic (PPK) analysis based principally on that is discussed below. In addition, a bioequivalence Study A15704 is also described below; the relevance of the bioequivalence study to this evaluation is uncertain, as discussed in the concluding summary of this section.

Qualitative PK aspects including distribution, elimination, metabolism, effects of subject characteristics and renal and hepatic dysfunction have not been specifically studied for YAZFlex in view of the identity of the tablets with other YAZ presentations.

Methods

Analytical methods

In Study A40196, serum concentrations of DRSP were determined by radioimmunoassay, and EE using a gas chromatography/mass spectrometry method. The lower limits of quantification (LLOQ) for measuring DRSP and EE concentrations were 0.10 ng/mL and 5.0 pg/mL, respectively. Similar methodology was used for DRSP in Study A15704, although with somewhat lower sensitivity (LLOQ 0.5 ng/mL).

Pharmacokinetic data analysis

In Study A15704, standard PK parameters including peak plasma concentration (C_{max}) and AUC were calculated and are detailed below. In Study A40196, longitudinal steady state

levels were obtained for DRSP and EE in a subgroup of treatment Group B (YAZ Extend - amounting to YAZFlex taken continuously), at Weeks 3, 7, 11, 14 and 17 of a cycle.

Statistical analysis

The computer modelling technique used in the cross-sectional PPK analysis is briefly described below.

When prespecified for testing as in Study A15704, bioequivalence was concluded if the 90% confidence intervals (CI) for the ratios of the geometric means of the two treatments being tested were entirely contained within the bounds 0.80-1.25 for both C_{max} and AUC.

Absorption

Bioavailability

Bioavailability was not assessed in the studies submitted with this application. It can be assumed that the bioavailability characteristics of the YAZFlex tablets are the same as those of the identically formulated YAZ tablets. Data on bioavailability of the constituents of YAZ has been assessed in previous clinical evaluation reports on YAZ and Yasmin.

Intra and inter individual variability

See comment below on conclusions of PPK analysis.

Pharmacokinetics in the target population

Subjects of the pivotal efficacy Study A40196 are representative of the target population, being women of childbearing age. In that study, two sets of PK measurements were taken; from the entire study population, samples were taken before and within 45 to 120 min following study drug administration at Visits 3 (Week 3) and 5 (Week 27). In addition to this extensive cross-sectional sampling, a longitudinal PK assessment was performed on a subgroup of subjects taking the fixed extended (YAZ Extend) regimen; while that product is not the subject of this evaluation, it can be regarded as such for PK purposes; if a subject taking YAZFlex does not have any unscheduled bleeding, she will take the product for the maximum cycle length of 120 days which creates a drug exposure situation identical to that of YAZ Extend in which the cycle length is fixed at 120 days. In this subgroup of 20 subjects, trough plasma levels of EE and DRSP were measured on samples taken before study drug administration at Weeks 3, 7, 11, 14 and 17 of a 120 day (17 week) cycle. The results, expressed as mean (standard deviation (SD)) were as summarised in Table 5.

Table 5. Plasma concentrations of EE and DRSP.

	n n	EE (pg/mL) DRSP (ng/mL)
Week 3	19 20	18.8 (8.2) 23.1 (5.3)
Week 7	19 19	17.3 (4.4) 25.5 (6.8)
Week 11	19 19	17.3 (4.2) 27.0 (6.7)
Week 14	18	17.5 (4.6)

	n n	EE (pg/mL) DRSP (ng/mL)
	19	25.5 (7.0)
Week 17	19 19	21.6 (10.3) 28.9 (9.6)

The PK measurements from the wider clinic population were used for the development of the PPK; altogether, following exclusion of samples subject to protocol deviations, this comprised for EE 4218 observations from 1109 subjects and for DRSP 4042 observations from 1096 subjects. For each sample, the dataset was informed by the exact time since last dose of study drug and contained covariate information including age, body weight, race, smoking and alcohol history. The variance in time between drug administration and sampling enable construction of time versus concentration profiles by integrating the data from the entire population; the complex computer modelling procedures involved in the construction of the PPK model were fully described in the sponsor's report. For the purpose of this evaluation report, relevant findings include:

- Significant individual variation in exposure; the observed range for AUC for 90% of the study population was, for DRSP, 569-1345 ng.h/mL and for EE 506-1434 pg.h/mL.
- For both component drugs, clearance increased with body weight so that for a notional subject weighing 79.8 kg exposure was 17.2% lower for DRSP and 15.3% lower for EE compared with a 51 kg subject.
- Clearance also increased with age for EE, for which exposure at age 34 was found to be 11.2% lower compared with that at age 19.
- Most importantly for this evaluation, no differences in drug exposure were found between the treatment groups YAZFlex, YAZ Extend and YAZ.

By comparison with the intrinsic between-individual variability, the variances observed in relation to weight and age do not appear clinically relevant.

Exposure relevant for safety evaluation

PK data presented in this section were derived from pivotal efficacy and safety Study A40196. The data from Study A15704 are not relevant as they involved the administration of DRSP alone to a small group (14) of menopausal women not representative of the target population. Accordingly there is no additional safety exposure deriving from PK studies.

Evaluator's overall conclusions on pharmacokinetics

The PK data from pivotal Study A40196 shows that steady state exposure to the components of YAZFlex, DRSP and EE, is qualitatively similar to that found for the pharmaceutically identical product YAZ in previous studies. It also shows that steady state exposure of both component drugs is maintained throughout the maximum 120 day cycle of YAZFlex. In a controlled parallel group situation, the exposure characteristics of YAZFlex are not distinguishable from those of the existing registered product YAZ. The high degree of population variance in exposure to both component drugs applies equally to YAZ as to YAZFlex. Overall, the studies indicate no pharmacokinetic differences between YAZFlex and YAZ.

It is not clear why bioequivalence Study A15704 was presented for evaluation with this application.

Pharmacodynamics

The pharmacodynamics of DRSP and EE in relation to the contraceptive and other ovarian suppressive actions of YAZ or YAZFlex have been well described in previous clinical evaluation reports (CERs) and have no bearing on the findings of this evaluation report.

Efficacy

Introduction

Efficacy of YAZFlex has to be considered in respect of the three proposed indications; contraception, acne and PMDD. The new data submitted by the sponsor (Studies A40196, A48294, and A47505) principally support the contraception indication and are discussed below. Consideration of the *acne and PMDD indications* will be based on validating that exposure to the active constituents of YAZFlex and YAZ is sufficiently similar between the two treatments that the data which supported these indications for YAZ can be applied to YAZFlex. This is discussed in the conclusion to this section.

Pivotal clinical studies A40196 and A48294

Methods

Objectives

The objectives of both these studies were to demonstrate that use of the extended cycle format of YAZ (YAZFlex) was not associated with any loss of contraceptive efficacy, while reducing the frequency and amount of menstrual bleeding and thereby constituting a product more satisfactory to the user; and that this could be achieved without compromising safety.

Study participants

Participants were healthy female volunteers requesting contraceptive protection. In Study A40196 which was conducted in European and Canadian centres (the majority in Germany), an age limit of 18-35 was used. In the US Study A48294, the age limit was 18 to 45 years.

Treatments

All subjects were treated with YAZ products as described above. Each study had three asymmetric treatment arms, with the majority of subjects being randomised, or in the case of Study A48294 assigned, to YAZFlex. Each study had an active control arm in which the treatment was YAZ. The third arm received YAZ Extend in Study A40196 and YAZ Stop& Go in Study A48294. No subjects received placebo.

Outcomes/endpoints

The sponsor's hypothesis for benefit in introducing the extended cycle preparation was that there be firstly maintenance of contraceptive efficacy and secondly, a reduction in the number of bleeding days per unit time. Consistent with this, the primary efficacy variables in pivotal Studies A40196 and A48294 were the unintended pregnancy rate (Pearl Index and life-table analysis), and in Study A40196 the total number of bleeding days; in Study A48294 , bleeding pattern and cycle control are classified as secondary outcome measures. Secondary objectives were to enhance user convenience and to reduce the incidence of problems associated with menstruation such as dysmenorrhoea, headache, and breast symptoms, and the secondary efficacy variables assessed reflect this. In addition, a subgroup of subjects in Study A40196 underwent assessment for bone density loss and measurement of biochemical bone markers.

For contraceptive efficacy, the Pearl Index is calculated as the number of pregnancies/100 years of woman-use[3]. This may be calculated as a raw index, or as a 'corrected' or 'adjusted' index. In the latter case, the numerator of the equation (number of pregnancies) is reduced by removing those instances classed as subject failures (mostly attributed to lack of compliance), leaving only instances classed as method failures. When performing this adjustment, the denominator (total exposure) has to be reduced by removing the exposure related to subject failures. These procedures have been carried out in the efficacy studies. Contraceptive efficacy is also measured in these studies by life-able analysis using the Kaplan Meier estimator.

With 'correct use' (full compliance), Pearl Index values of <1 are expected in users of combined oral contraceptives (COC), whereas with 'typical use', values may be in the range 1 to 33.

The assessment of *bleeding patterns* in the efficacy studies was an extremely complex process and reflects the relationship of these outcome measures to user satisfaction with the product. For the woman using an oral contraceptive, particularly in an extended cycle regimen, parameters of interest in relation to bleeding relate to the *amount* and to *timing*: an ideal result will be the least possible amount of bleeding, on days which are entirely predictable, and in the case of a flexible regimen such as proposed in this application, to some extent adjustable to comply with lifestyle requirements. In clinical practice, a distinction is usually drawn between *withdrawal bleeding* which typically occurs during or following the tablet free interval in a cyclical preparation, and *breakthrough bleeding* which occurs during the period of active tablet administration. This is an expected feature of the continuous progestogen only oral contraceptives (OCs), and is also more frequently observed in COCs containing smaller doses of oestrogen.

Consistent with the above background, the protocol of the efficacy studies distinguishes between 'scheduled' or 'withdrawal' bleeding on the one hand, and 'intracyclic' or 'unscheduled' bleeding on the other. These terms are used to some extent interchangeably which does create some confusion for the reader. One important matter of definition is that 'unscheduled' bleeding which meets the criterion for triggering a 4 day tablet free interval with the use of YAZFlex becomes defined as part of the 'scheduled' withdrawal bleed which then follows that tablet free interval. In other words, an episode which would be regarded as breakthrough bleeding by a woman using a continuous regimen is managed by stopping the tablets for 4 days, having a period, and then commencing a new cycle, as is commonly advised in existing clinical practice.

A summary of the definitions used to define withdrawal bleeding episodes and distinguish them from intracyclic bleeding, with graphically displayed examples of their application was provided in the submission.

Sample size

The calculations for sample size in Study A40196 were described in the study report. It describes previous experience with cycle control studies as suggesting that a group size of a minimum of 200 volunteers per treatment arm would be sufficient to describe differences in bleeding patterns. A planned size of 660 subjects was allocated to the YAZFlex arm as this was the 'preferred' regimen, and also needed to be tested for contraceptive efficacy. Some 225 subjects were allocated each to the YAZ Extend and YAZ arms; the report indicates that assuming a difference between the groups of 10 in number of bleeding days, a standard deviation (SD) of 28 days and drop-out of 40%, these sample sizes would lead to a power of at least 94% to demonstrate superiority of the YAZFlex regimen in relation to bleeding patterns.

[3] McGraw-Hill Concise Dictionary of Modern Medicine. (2002)

For contraceptive efficacy (Pearl Index), the statistical analysis plan describes calculating the sample size in compliance with the requirements of the TGA adopted EU guidelines on clinical investigation of steroid contraceptives in women[4]. The calculation assumed that the extended regimen would be at least equal in contraceptive efficacy to the standard (YAZ) regimen, and determined that a sample size of 885 women would estimate the Pearl Index with an upper 90% confidence limit not exceeding the point estimate by more than 1, if the true value was 0.85.

Similar calculations are described for the other two sponsor-supervised efficacy studies in the application.

Randomisation

Randomisation for all the described efficacy studies was carried out by the central randomisation group at Bayer Pharma AG using the software package Statistical Analysis System (SAS).

Blinding (masking)

All of the efficacy studies in the application, including supportive Study A47505, were of necessity open label because of the nature of the comparison between user-managed menstrual cycle regimens.

Statistical methods

The statistical method for determining confidence interval for Pearl Index has been described above. For all other quantitative parameters to do with bleeding days and cycle control, standard descriptive statistics were determined and comparison undertaken between the test and reference groups using the t-test.

Results

Participant flow and numbers analysed

Details of the numbers of subjects screened and randomised were given in the individual study reports. A summary of the numbers of subjects in the full analysis (FAS) and per protocol (PPS) sets is shown below for both pivotal studies and also supporting Study A47505; the percentage figures are % of all subjects randomised or assigned to the various treatments.

[4] Guideline on Clinical Investigation Of Steroid Contraceptives In Women. EMEA/CPMP/EWP/519/98 Rev 1

Table 6. Subject numbers in submitted studies. FAS and PPS.

By study

[a] Analysis sets:		FAS		PPS	
[b] Study A40196:	*two years* [c]		all women [d]		
	YAZ Flex$_{MB}$	888	(93.5%)	516	(54.3%)
[b] Study A40196:	*first year only*		all women [d]		
	YAZ Flex$_{MB}$	642	(92.9%)	314	(45.4%)
	YAZ Extend	209	(88.6%)	92	(39.0%)
	YAZ	216	(90.4%)	142	(59.4%)
Study A48294:			all women		
	YAZ Flex$_{MB}$	1406	(98.9%)	295	(20.8%)
	YAZ Stop&Go	232	(99.1%)	119	(50.9%)
	YAZ	226	(97.4%)	103	(44.4%)
			women 18 to 35 years of age		
	YAZ Flex$_{MB}$	1406	(98.9%)	295	(20.8%)
	YAZ Stop&Go	202	(99.0%)	105	(51.5%)
	YAZ	198	(97.5%)	90	(44.3%)
Study A47505:			all women		
	YAZ Flex$_{MB}$	115	(96.6%)	92	(77.3%)
	YAZ	108	(96.4%)	100	(89.3%)

The large proportion of exclusions from the PPS mainly reflects minor protocol deviations relating to cycle dates.

Recruitment

No details of recruitment procedures are given but the sole initial criterion for the pivotal studies was 'women of childbearing age requesting contraception', from which it is assumed that some form of public advertisement may have been used.

Conduct of the studies

In both studies, parallel group treatment was continued for one year during which bleeding patterns and cycle control were compared between the YAZFlex groups and the comparator groups comprising YAZ, YAZ Extend (in Study A40196) and YAZ Stop&Go (Study A48294). In Study A40196 only, there was an observational extension period of a further year during which all participating subjects who wished to do so could continue, taking YAZFlex in all cases. Pregnancy data was collected throughout Years 1 and 2.

Note that randomisation between the YAZFlex and comparator groups only occurred in Study A40196. In Study A48294, the majority of recruited subjects were assigned to YAZFlex and the remainder randomised between the two comparator arms. The reasons for this was not entirely clear to the evaluator but may have been related to the timing of a requirement by the FDA for inclusion of the YAZ Stop& Go arm.

Outcomes and estimation

Unadjusted Pearl Index in Study A40196 was 0.64 with 95% CI 0.28, 1.26 and in Study A48294 it was 1.65 with 95% CI 0.96, 2.65. In Study A40196, a further Pearl Index calculation was carried out based on the first year of treatment only and including any pregnancy with a conception date within 14 days after the end of study medication. This resulted in an estimate of 0.34 (95% CI; 0.04, 1.23). Additionally, cumulative failure rate (probability of pregnancy occurring) was calculated, using the Kaplan Meier estimator, at 0.0128 (95% CI; 0.0062, 0.0266), indicating the probability of contraceptive protection to be 98.72%. The sponsor comments that the probability estimate for pregnancy is higher than the Pearl Index because exposure is exclusive of subjects who dropped out before the last pregnancy occurred. Estimated cumulative failure rate using this methodology in Study A48294, with 95% CI, was 1.63% (1.01, 2.61). In this study, pregnancy data was also calculated for the pooled YAZFlex/ YAZ Stop& Go population. Unadjusted Pearl index was

1.92 (95% CI; 1.22, 2.89) and estimated cumulative failure rate 1.83% (95% CI; 1.21, 2.75).

Adjusted Pearl Index in Study A40196 was 0.60 but in Study A48294 it was 5.36; this value is felt to be artefactual.

As already indicated, the sample sizes in the comparator arms of these studies were not designed to permit a reliable Pearl Index calculation but the numbers of pregnancies occurring suggest an unintended pregnancy risk of the same order as with YAZFlex.

Bleeding patterns are analysed in both studies using the criteria described above. In Study A40196, YAZFlex subjects on average had 62% as many bleeding days as YAZ subjects. The difference was highly significant ($p<0.0001$, Student's t-test) but does contain the implication that they had more bleeding per cycle, as YAZFlex subjects only had 38% as many cycles as YAZ subjects. An important secondary observation is that YAZFlex subjects also had less bleeding days; on average 41 compared with 61 for YAZ Extend subjects.

For the per protocol analysis set, the results were similar: the mean number of bleeding days per YAZFlex subject was 38.6 days, 56% of the average 68.7 days recorded by YAZ subjects, and 70% of the average 55.2 days for YAZ Extend subjects.

Another important variable, the mean length of withdrawal bleeding, is summarised in Table 7 below; the mean length of withdrawal bleeding over the first two extended cycles, by comparison with the monthly cycles for the YAZ subjects.

Table 7. Mean length of withdrawal bleeding.

Group	Length of withdrawal bleeding
Group A (YAZFlex)	7.5-9.8 days
Group B (YAZ Extend)	9.8-10.5 days
Group C (YAZ)	4.4-5.2 days

YAZFlex subjects also had less unscheduled, intracyclic bleeding than YAZ Extend subjects.

In Study A48294, the frequency of *bleeding and spotting episodes,* effectively, what the subject would call a period, which by the nature of the treatment regimens is relatively fixed for YAZ but variable for the other two treatments, is shown in the following table, expressed as the mean with estimates of variance per 120 day reference period (Table 8).

Table 8. Bleeding and spotting periods.

Treatment	Reference Period	n	Mean	SD	Min	Q1	Median	Q3	Max
YAZ Flex	1	992	2.5	2.0	0	1.0	2.0	3.0	16
	2	867	2.5	1.9	0	1.0	2.0	3.0	18
	3	793	2.4	2.1	0	1.0	2.0	3.0	20
YAZ Stop&Go	1	166	3.1	2.2	0	1.0	3.0	5.0	9
	2	156	2.8	2.0	0	1.0	2.0	4.0	10
	3	141	2.5	2.4	0	1.0	2.0	3.0	20
YAZ	1	150	4.2	1.4	0	4.0	4.0	5.0	10
	2	134	4.1	1.3	0	4.0	4.0	5.0	9
	3	111	4.0	1.4	0	4.0	4.0	4.0	10

A reduced frequency of bleeding episodes is shown for each extended regimen, by comparison with the standard YAZ regimen. The reduction is greater for YAZFlex than for YAZ Stop&Go as the latter regimen allows elective episodes.

After two completed cycles of treatment, the mean length of bleeding per cycle was as shown in Table 9 below.

Table 9. Mean length of bleeding per cycle

Group	Mean length of bleeding per cycle
YAZFlex	7.7 - 8.7 days
YAZ Stop&Go	6.8 - 9.4 days
YAZ	4.6 - 5.2 days

In summary, both pivotal studies show that women using YAZFlex had significantly less bleeding days, less frequent episodes of bleeding but longer periods of withdrawal bleeding than women using the standard cyclical preparation YAZ.

Ancillary analyses

In Study A40196 at screening, 24.9% of subjects were recorded as experiencing dysmenorrhoea and 4.9% intra-cyclic bleeding. Questionnaire assessment regarding menstruation related symptoms through the study was documented in the study report. Mild abdominal or pelvic pain was recorded by 46% of subjects at baseline and this was reduced to 29% at 39 weeks. Likewise the prevalence of menstruation related backache was reduced from 25% to 17%. Other aspects including effects on daily life and sexual activity were also improved. These observations are, of course, uncontrolled.

Subject satisfaction was high in Study A40196, with 62% of YAZFlex subjects reporting 'very satisfied' and 86% indicating preparedness to recommend the regimen to a friend. This does reflect the recruitment procedure which included interest in an extended cycle regimen. In Study A48294, satisfaction surveys indicated a high degree of satisfaction with the extended cycle length, the ease of following the regimen and the instructions. There was a low degree of concern that contraceptive reliability might be compromised.

Clinical studies in special populations

The included clinical studies have been carried out on the population of concern, women of contraceptive age. No sub analyses have been performed for demographic factors such as race or ethnicity. The CER for YAZ describes no influence of race on PK and it seems unlikely that such factors are relevant to the findings of this evaluation.

Analysis performed across trials (pooled analyses)

Pooled analyses of data from the pivotal studies were provided in the sponsor's Summary of Clinical Efficacy; the data sets for these analyses are shown below (Table 10). The FAS is shown in the left-hand column and the PPS on the right, the % figures indicating each population figure as a proportion of all subjects randomised or assigned to the particular treatment.

Table 10. Pooled analyses

Pooled data [e]				
Studies A40196 and A48294:		all women		
	YAZ Flex$_{MB}$/YAZ Stop&Go	2526 (97.0%)	930	(35.7%)
	YAZ Flex$_{MB}$	2048 (97.0%)	609	(28.8%)
	YAZ	442 (93.8%)	245	(52.0%)
		women 18 to 35 years of age		
	YAZ Flex$_{MB}$/YAZ Stop&Go	2496 (96.9%)	916	(35.6%)
	YAZ Flex$_{MB}$	2048 (97.0%)	609	(28.8%)
	YAZ	414 (93.7%)	232	(52.5%)

The overall unadjusted Pearl Index for the entire YAZFlex/YAZ Stop&Go population of 2526 subjects was 1.25 (upper 95% CI, 1.78). A pooled figure for YAZFlex subjects alone is not given but would be little different. The pooled figure is significantly influenced by the Pearl Index for Study A48294 which as shown above was 1.65 compared with that for A40196 which was 0.63. The disparity between the two studies is at least partly explained by compliance. To the criterion of cycles having at least 24 days of tablet intake, compliance was higher in the EU/Canada Study A40196 (approximately 95% of cycles for 88% of women) than in the US Study A48924 (approximately 93% of cycles for 82% of women), as was compliance to the criterion cycle length between 24 and 124 days (EU/Canada study with 93% of cycles for 80% of women; US study with 89% of cycles for 65% of women).

The following table (Table 11) shows the parameters relating to bleeding days for the pooled population.

Table 11. Bleeding days. Pooled analysis.

Study	YAZ Flex$_{MB}$					YAZ					YAZ Stop&Go					YAZ Extend				
	n	Mean	± SD	Median	[Min-Max]	n	Mean	± SD	Median	[Min-Max]	n	Mean	± SD	Median	[Min-Max]	n	Mean	± SD	Median	[Min-Max]
FAS																				
Number of bleeding and spotting days																				
A40196 [a]	640	**41.0**	±29.1	**34.0**	[2 – 219]	215	**65.8**	±26.9	**68.0**	[5 – 161]		*Not applicable*				209	**60.9**	±51.1	**45.0**	[1 – 298]
A48294	1317	**39.9**	±29.6	**34.0**	[0 – 284]	207	**51.8**	±34.6	**53.0**	[1 – 216]	222	**46.8**	±33.1	**41.0**	[1 – 208]		*Not applicable*			
Pooled	1957	**40.3**	±29.5	**34.0**	[0 – 284]	422	**58.9**	±31.7	**60.5**	[1 – 216]		*Not applicable*					*Not applicable*			
Number of bleeding-only days																				
A40196 [a]	640	**20.8**	±15.2	**18.0**	[0 – 115]	215	**43.4**	±20.0	**46.0**	[0 – 96]		*Not applicable*				209	**23.8**	±24.5	**17.0**	[1 – 208]
A48294	1317	**19.4**	±15.7	**16.0**	[0 – 163]	207	**32.9**	±23.5	**33.0**	[0 – 158]	222	**21.4**	±15.6	**18.0**	[0 – 87]		*Not applicable*			
Pooled	1957	**19.8**	±15.5	**16.0**	[0 – 163]	422	**38.3**	±22.4	**40.0**	[0 – 158]		*Not applicable*					*Not applicable*			
PPS																				
Number of bleeding and spotting days																				
A40196 [a]	314	**38.6**	±25.1	**32.5**	[3 – 162]	142	**68.7**	±24.2	**69.0**	[11 – 156]		*Not applicable*				92	**55.2**	±43.9	**43.0**	[1 – 186]
A48294	295	**38.5**	±23.1	**34.0**	[1 – 114]	103	**58.3**	±31.3	**58.0**	[1 – 216]	119	**44.5**	±32.9	**35.0**	[3 – 159]		*Not applicable*			
Pooled	609	**38.6**	±24.1	**33.0**	[1 – 162]	245	**64.4**	±27.9	**64.0**	[1 – 216]		*Not applicable*					*Not applicable*			
Number of bleeding-only days																				
A40196 [a]	314	**19.5**	±14.3	**16.0**	[1 – 115]	142	**45.7**	±19.2	**48.0**	[0 – 96]		*Not applicable*				92	**21.4**	±19.7	**17.0**	[1 – 117]
A48294	295	**18.9**	±12.7	**16.0**	[0 – 77]	103	**37.3**	±23.7	**39.0**	[0 – 158]	119	**20.2**	±15.9	**17.0**	[0 – 87]		*Not applicable*			
Pooled	609	**19.2**	±13.6	**16.0**	[0 – 115]	245	**42.2**	±21.6	**43.0**	[0 – 158]		*Not applicable*					*Not applicable*			

The data for numbers of bleeding days are similar between the pooled and individual studies and the hierarchy of numbers of days with respect to the different treatment arms remains the same.

Return to fertility

The protocol for Study A40196 required that women who wished to become pregnant, either at the end of the study or as a reason for premature discontinuation, be followed up for one year and be then invited to complete a questionnaire regarding outcome. Of 26 women aged 23 to 34 years who reported posttreatment pregnancies, 18 had been treated

with YAZFlex, 2 with YAZ Extend and 5 with conventional YAZ. These data, although limited, appear in proportion with the overall numbers of subjects treated and suggest that the extended cycle regimen does not impede subsequent fertility.

Supportive Study A 47505

This parallel group study, evaluated symptomatology related to dysmenorrhoea in 115 subjects randomised to the YAZFlex regimen by comparison with 108 subjects randomised to YAZ. Enrolled subjects were required to meet preset criteria on pain scores related to menstruation. Data on numbers of bleeding days and frequency of bleeding episodes were similar to those in the pivotal efficacy studies. The principal finding was a reduced frequency of dysmenorrhoea. As the extended cycle regimen of YAZFlex results in less frequent menstruation, this was obviously a likely finding. On low level, subjective evidence, both YAZFlex and YAZ improved the overall dysmenorrhoea assessment which again is not a surprising finding as this is a documented effect of oral contraceptive administration and the two regimens are qualitatively similar on a per cycle basis. There is no persuasive evidence that YAZFlex, by comparison with YAZ, brings about additional improvement in the intensity of dysmenorrhoeic symptoms, as opposed to the reduction in frequency of the menstrual episodes which precipitated the symptoms.

Evaluator's overall conclusions on clinical efficacy

Oral contraception

The best comparator for the contraceptive efficacy of YAZFlex is the data from the TGA CER for YAZ. In pivotal Study A12007, the unadjusted Pearl Index was 1.29 with an upper 97.5% confidence limit of 2.30, gathered from 11,140 cycles of treatment. The adjusted Pearl Index, restricted to cases considered as method failures, was 0.72 with an upper 97.5 confidence limit of 1.69, based on 9,010 cycles of treatment. The one-year pregnancy rate according to Kaplan-Meier life table analysis is given as 1.26% with 95% CI of 0.52%, 2.01%. For the sponsor's related oral contraceptive (OC) product Yasmin, unadjusted Pearl index was 0.70. These values closely resemble the outcomes for the pooled analysis of contraceptive efficacy from the two pivotal studies shown above.

Comparing the results of the two pivotal studies included in the present application, it is clear, as is well established in the literature, that medication compliance is the major factor in optimising the efficacy of combined OC (COC) pill. In Study A40196, in which compliance was better than in Study A48294, the unadjusted Pearl Index was 0.64 and the one-year pregnancy rate 1.28%. Taking these data together with the observations on YAZ in the previous paragraph, and comparing as far as possible true method failures in these separately conducted studies, it is clear, even though there is no formal statistical test of equivalence, that the extended cycle YAZFlex regimen is equivalent to YAZ in terms of contraceptive efficacy.

For women who wish to have extended cycles and/or control the timing of their menstrual cycles, YAZFlex is of superior efficacy in reducing the overall number of bleeding days and improving user satisfaction.

Treatment of moderate acne vulgaris in women who seek oral contraception

No new data is presented by the sponsor regarding this indication. It is not specifically addressed in either of the pivotal efficacy studies. Included in the current submission is a (sponsor's) Summary of Clinical Efficacy (acne). This describes the YAZFlex regimen at the beginning of the introductory section but otherwise only presents and summarises data which were contained in the YAZ application and have been previously evaluated by the TGA with a positive recommendation, although with the caveat that the product should only be used for this indication

'in women at least 14 years old who have achieved menarche and who choose to use oral contraceptives for birth control'.

The rationale for use of COCs in the treatment of acne is that in addition to suppressing ovulation they suppress the production of ovarian hormones including androgens. This effect is not associated with the role of the COC in respect of cycle control and it is the expectation of this evaluator that suppression of androgen secretion would be maintained throughout the extended cycle regimen. The ultimate proof of this would be demonstration of suppressed plasma testosterone in subjects taking YAZFlex. The study protocol describes subgroups of approximately 25 subjects per treatment group in whom hormone levels including testosterone were determined. The results were not discussed in any detail in the study report. Baseline serum testosterone (ng/mL, mean ± SD) was 0.74±0.27 in the YAZFlex and 0.72±0.32 in the YAZ subjects. These values fell to 0.43±0.17 and 0.35±0.20 respectively at Week 11 and were 0.42±0.12 for the YAZFlex and 0.35±0.19 for the YAZ subjects at Week 51. There is no statistical analysis but the data shows an approximate 50% suppression in both groups with no significant difference in response between the groups as far as can be judged from the variance values. The suppression is slightly less for YAZFlex but this is apparent as early as Week 3, by which stage the two regimens remain identical. The important observation is that the suppression was maintained throughout the 12 month treatment period just as well in the extended cycle regimen as with the standard regimen. This biochemical data assists the conclusion that there is no reason to expect the YAZFlex regimen to be any less efficacious than the conventional YAZ regimen for the control of acne.

Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraceptives as their method of birth control

For the extension of this indication from YAZ to the extended cycle preparation YAZFlex, there is a complete lack of information in the current submission. The letter of application provides no guidance beyond the statement that '*the proposed indications for YAZFlex are the same as the approved indications for YAZ*'. Whilst there were specific sponsor Summaries of Clinical Efficacy included for the contraceptive and acne indications, as referred to above, there is none for the PMDD indication. The sponsor's Clinical Overview, an undated but reasonably recent document containing references to 2009 literature, has sections on the other two indications but that makes no reference to PMDD and states that 'the investigational product YAZFlex was developed as an OC with the additional indication '*treatment of moderate acne vulgaris only in women seeking oral contraception*'.

This indication was approved by TGA for YAZ based on support by the clinical evaluation process, backed up by two specific clinical studies. An independently published literature review[5] also provides support for the use of a low dose EE/DRSP formulation (presumably YAZ) in PMDD, although commenting that a large placebo effect was evident.

Hypothetically, sufferers from PMDD should be helped by an extended cycle preparation such as YAZFlex. As the name of the condition suggests, its symptoms occur predominantly in the premenstrual period and should be less troublesome or at least less frequent if episodes of menstruation are suppressed. The pathophysiology of PMDD is so poorly understood, however, that this cannot simply be assumed. There is some support in the literature that cyclical mood symptoms decrease with the use of extended cycle OC preparations[6,7] but not specifically in patients who meet the diagnostic criteria for PMDD.

[5]Oral contraceptives containing drospirenone for premenstrual syndrome. Lopez LM, Kaptein AA, Helmerhorst FM. Cochrane Database Syst Rev. 2009

[6]Effects of continuous versus cyclical oral contraception: a randomized controlled trial. Legro RS, Pauli JG, Kunselman AR, Meadows JW, Kesner JS, Zaino RJ, Demers LM, Gnatuk CL, Dodson WC. J Clin Endocrinol Metab 93(2):420 (2008)

[7]Long-term assessment of symptomatology and satisfaction of an extended oral contraceptive regimen. Coffee AL, Sulak PJ, Kuehl TJ. Contraception 75(6):444 (2007)

While it appears likely that women with PMDD may be helped by YAZFlex, approval of this indication should be supported by specific evidence of efficacy.

Safety

Introduction

This safety evaluation should be regarded as incremental to that of the original YAZ preparation. The short term safety profile and spectrum of potential safety issues for YAZFlex can be assumed to be the same as for YAZ as both the daily dosage and characteristics of the exposed population are identical. Exposure over time to the constituents of the formulation is within 5 to 10% of that for the conventional YAZ preparation. Safety issues needing to be considered by this evaluation are those which follow from the extended menstrual cycle which characterises the YAZFlex regimen. These include endometrial safety and any potential systemic effects which might arise from longer periods, up to 120 days, of continuous administration of EE or DRSP.

Patient exposure

The three clinical studies presented in this application involved a total of 2409 women exposed to YAZFlex. In Study A40196, 642 women were initially randomised to YAZFlex and of these 83.9% completed the first year of treatment. Of the whole study population, 783 women entered, and 681 completed, Year 2 on YAZFlex. Study A48294 included 1406 women on YAZFlex, of whom 61.6% completed 12 months treatment. This safety population adds substantially to the 1337 women treated with YAZ for an average of 9.9 cycles, as reviewed in the original YAZ CER. The sponsor's Summary of Clinical Safety describes a comparison of safety data from the two pivotal studies, including all extended cycle subjects (YAZFlex, YAZ Extend, and YAZ Stop&Go), referred to as the YAZFlex safety pool, with data from the subjects in these studies who received YAZ (YAZ pool). Such a comparison is of particular relevance to this evaluation, although it is limited in extent and this is commented on below. The small number of subjects from Study A47505 was quite reasonably not included in the pooled analysis because of demographic and recruitment differences. The sponsor's Summary of Clinical Safety also presents lengthy, comprehensive narratives of the existing safety data from the studies previously presented for evaluation but does not attempt a formal comparison of these data with that obtained on the YAZFlex subjects in Studies A40196 and A48294. The comparator (YAZ) group for the safety evaluation of YAZFlex therefore consists of the subjects who received YAZ in these newly presented pivotal studies. Although relatively small in number (226), they are at least comparable in terms of demographic characteristics and treatment assignment/randomisation.

Women receiving YAZFlex do have a greater individual exposure to the constituent medications over time as a result of the reduced number of tablet free intervals implicit in the regimen. This is, however, of relatively minor degree. Subjects on YAZFlex had on average 2.5 tablet free intervals over 120 days compared with 4.1 for YAZ subjects. Based on this, mean individual exposure over the 120 day period was 6.2% higher for the YAZFlex subjects. A subject taking a full 120 day cycle without interruption, which was unusual in the YAZFlex studies but would be mandatory with YAZ Extend, would have an increase in exposure of 11.1%. These amounts are within the range of intra-individual variance seen in the PK studies and would not seem likely to be of clinical significance.

Adverse events

In the pivotal studies, safety evaluations consisted of collecting data on adverse events (AE) and serious adverse events (SAE) and routine physical examination findings

including gynaecological examination; and in subgroups of Study A40196, endometrial histology (by biopsy) and morphology and thickness by transvaginal ultrasound (TVU); measurement of metabolic variables including plasma lipids, carbohydrate tolerance and haemostatic parameters, and levels of reproductive hormones.

The AE profile for the 'pooled' analysis of YAZFlex and YAZ subjects is shown below in Table 12.

Table 12. AEs. Pooled analysis of YAZFlex and YAZ subjects.

	A48294						A40196 (Years 1 & 2) [a]					
	YAZ Flex N=1406		YAZ Stop&Go N=232		YAZ N=226		YAZ Flex N=888		YAZ Extend N=209		YAZ N=216	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
No. (%) of women with any AE	870	(61.9%)	167	(72.0%)	157	(69.5%)	605	(68.1%)	150	(71.8%)	151	(69.9%)
No. of AEs	2233		415		394		2385		629		633	
AE relationship [a]												
Related	285	(20.3%)	37	(15.9%)	46	(20.4%)	163	(18.4%)	72	(34.4%)	59	(27.3%)
AE intensity												
Mild	321	(22.8%)	56	(24.1%)	59	(26.1%)	219	(24.7%)	45	(21.5%)	47	(21.8%)
Moderate	449	(31.9%)	85	(36.6%)	79	(35.0%)	308	(34.7%)	69	(33.0%)	72	(33.3%)
Severe	87	(6.2%)	25	(10.8%)	16	(7.1%)	63	(7.1%)	34	(16.3%)	30	(13.9%)
Not applicable	1	(<0.1%)	0	-	0	-	2	(0.2%)	0	-	0	-
Not done / Unknown	12	(0.9%)	1	(0.4%)	3	(1.3%)	13	(1.5%)	2	(1.0%)	2	(0.9%)
Deaths	0	-	0	-	1	(0.4%)	0	-	0	-	0	-
Serious AEs (SAEs)	12	(0.9%)	6	(2.6%)	2	(0.9%)	22	(2.5%)	5	(2.4%)	2	(0.9%)
Discontinuations due to AEs	92	(6.5%)	13	(5.6%)	11	(4.9%)	49	(5.5%)	26	(12.4%)	10	(4.6%)

There is no consistent pattern of difference between the extended cycle and conventional regimens in any of the display parameters.

As the sponsor's Summary of Clinical Safety did not appear to contain a clear and concise summary of comparison of specific classes of AE between the 'YAZFlex pool' and general body of safety data on YAZ, reference is made to the individual pivotal study reports for this information. In the original as well as the current application, AE of specific interest are identified as those relating to venous thromboembolism (VTE), cardiovascular events, and cancer.

In Study A40196 the most commonly reported AE were headache, breast pain, nausea and dysmenorrhoea. These events were most common in the YAZ group, reflecting the increased incidence of menstruation in that group.

Serious adverse events and deaths

In Study A40196, 23 SAE were reported by 19/642 (3.0%) of YAZFlex subjects, 9 by 7/209 (3.3%) YAZ Extend subjects and 3 by 3 (1.4%) YAZ subjects. Some bias in reporting might be suggested as this was an open study but most of the events were significant clinical issues which should have come to notice irrespective of the trial situation. The apparent imbalance towards the extended cycle groups is contributed to by a number of seemingly unrelated events (such as appendicitis, renal colic, chlamydia infection, vulval abscess, asthenia, non-specific abdominal pain, foot fracture, ligament rupture) but one area of potential concern is *the occurrence of three confirmed cases of venous thromboembolism (VTE)*. Two of these were major episodes which occurred spontaneously while taking YAZFlex. One of the subjects had an underlying risk factor in being positive for Factor 2 and Factor 5, mutations known to predispose to thrombosis. Both had a history of previous administration of EE/DRSP oral contraceptives. The third case, also taking YAZFlex, occurred post operatively following knee surgery.

Another subject on YAZFlex for 18 months was diagnosed with focal nodular hyperplasia of the liver after developing a rising alkaline phosphatase level. There was a history of two years OC use prior to the trial including six months on Yasmin.

In Study A48294**,** the overall incidence of SAE was lower (1.1%), with no difference in incidence between the YAZFlex and YAZ groups. There were a further two cases taking YAZFlex who were **suspected** of deep vein thrombosis (DVT). In the first case, there was a fairly clear cut diagnosis of superficial thrombophlebitis which responded to appropriate treatment. In the second case, the clinical presentation was more suggestive of DVT but, as with the first case, an apparently thorough ultrasonographic assessment revealed no confirmatory evidence and the patient responded to conservative treatment without anticoagulation.

The overall exposure of subjects taking YAZFlex in the two pivotal studies combined is 2085 women-years (WY) for subjects completing the 12 month study periods. Adding a moiety of 415 WY for those subjects who discontinued prematurely, which is a conservative estimate (exact figure not accessed from study reports), yields an exposure base of 2500 WY. The cases described above amount to 3 definite VTE episodes (one postoperative), and 1 possible. Depending on criteria for inclusion, there are therefore either 3 or 4 cases at that exposure yielding an incidence of VTE episodes of either 1.2 or 1.6/1000 WY. Estimates of the incidence of VTE in DRSP-containing OC preparations have been published by both the European Active Surveillance Study (EURAS) and the US Ingenix study, both discussed below. The EURAS estimate was 0.91/1000 WY and the Ingenix estimate was 1.3/1000 WY (sponsor's Summary of Clinical Safety). The Ingenix estimate includes arterial events which are likely to be <10% of the total. Both sets of estimates have 95% CI spanning approximately 0.6-1.0/1000 WY, so the number of VTE episodes seen in the YAZFlex safety evaluation is consistent with the general experience of this serious adverse effect in the overall population of women using EE/DRSP (YAZ) preparations.

No deaths occurred during Study A40196, nor were there any cardiovascular events of concern in either study except for VTE. One subject in Study A48294 died in an aircraft accident.

A single case of breast cancer was reported in a YAZFlex subject in Study A48294. The reports also include one case of benign uterine leiomyoma in a subject taking YAZ.

Laboratory findings

Many of the laboratory parameters routinely measured showed changes commonly associated with OC administration, such as a rise in plasma insulin and minor changes in the plasma lipid profile. However, there were no changes of clinical significance or differences between the extended cycle and conventional regimens.

Twelve subjects in Study A40196 and 2 subjects in Study A48294 developed high serum potassium readings, an identified issue of concern due to the anti-mineralocorticoid activity of DRSP, and not specific to the extended cycle regimens. In all cases they seem to have recovered spontaneously; a number of the blood samples concerned were haemolysed so the finding was at least in some cases artefactual.

Endometrial biopsies were taken from a subgroup of subjects, 23 on YAZFlex and 17 on YAZ Extend, towards the end of the first year of Study A40196. There were no histologically abnormal findings; most biopsies showed inactive or atrophic endometrium with some 20% showing a secretory pattern.

Safety in special populations

No specific studies have been done in relation to YAZFlex. Safety relating to renal impairment, hepatic impairment, age, gender and ethnicity is summarised in the sponsor's Summary of Clinical Safety and is based on studies which were submitted with the original YAZ application already evaluated by the TGA.

Immunological events

None relevant; the same comment applies as for *Safety in Special populations* with regard to the previous evaluation by the TGA.

Safety related to drug-drug interactions and other interactions

None relevant; the same comment applies as for *Safety in Special populations* with regard to the previous evaluation by the TGA.

Discontinuation due to adverse events

In Study A40196, 78/1166 (6.7%) of subjects discontinued due to AE in Year 1; these comprised 6.1% of YAZFlex subjects, 11.0% of YAZ Extend subjects and 4.2% of YAZ subjects. Most withdrawals were related to symptoms commonly seen with OC administration including bleeding and spotting and menorrhagia, headache, nausea, irritability and migraine. The figures suggest that these symptoms were more prevalent with the longer extended cycles and are somewhat at odds with the efficacy data suggesting a reduction in menstruation related symptoms and the high degree of acceptability of the product. The finding may not be a real one as in Study A48294 , in which the overall incidence of AE and SAE was less, discontinuation due to AE were evenly distributed between the treatment groups. Alternatively, there may be a subpopulation at increased risk of development of these effects which was more strongly represented in the A40196 study population.

Postmarketing experience

There is no postmarketing experience with YAZFlex, which has yet to be marketed. However, in the context of the finding of this evaluation that the safety profile of YAZFlex is closely related to and in most respects indistinguishable from that of YAZ, safety surveillance of YAZ is relevant. The sponsor's Summary of Clinical Safety provides a comprehensive review of postmarketing surveillance of the company's EE/DRSP products which have been marketed since 2000 (Yasmin, Europe) and more recently in the form of YAZ (2006, United States). There is a particularly detailed review of the EURAS and Ingenix studies, mentioned above, in relation to VTE risk for DRSP containing OC by comparison with those containing levonorgestrel and other forms of progestogen. The data from these studies as presented in the sponsor's review suggest that VTE risk in these groups is comparable.

Evaluator's overall conclusions on clinical safety

With regard to the introductory comments made above, no differences are evident in either the nature or frequency of occurrence of AE reported in subjects using YAZFlex by comparison with control subjects using the conventional cyclical preparation YAZ. Some changes are evident in the distribution of common, menstrual cycle related symptoms; mostly these were experienced less commonly by subjects using the extended cycle preparation, but there may be a subgroup that subjectively reacts less well to this regimen. Both these observations are subject to selection bias in view of the open nature of the relevant studies.

Increased cumulative exposure to EE and DRSP is increased 5 to 10% with the use of YAZFlex by comparison with YAZ. This is not thought to be a level of concern. There is no evidence of endometrial safety being compromised by the extended cycle regimen.

The incidence of venous thromboembolism in the safety population using YAZFlex was within the range established for conventional cyclical EE/DRSP preparations and for OC generally, although as this is a rare side effect the statistical comparison cannot be made with confidence from the population size currently available for assessment.

All contraindications and precautionary statements applicable to YAZ should apply to YAZFlex on a continuing basis.

List of questions

Efficacy

The sponsor should be asked whether any evidence is available, or whether studies are in progress, to support the indication for use of the product in PMDD as discussed above.

Clinical summary and conclusions

Clinical aspects

Please refer to evaluator's summaries of pharmacokinetics, pharmacodynamics, clinical efficacy and clinical safety above.

Benefit risk assessment

The comments in this section do not refer to the intrinsic benefit or safety specifications of the YAZ or YAZFlex treatment regimens. They specifically comprise an assessment of incremental change in benefits and risk attributable to the characteristics of the YAZFlex regimen with reference to the existing approved fixed 28 day cycle YAZ regimen.

The sponsor's risk management plan (RMP) is an extensive 185 page document including comprehensive reviews of the literature particularly relating to established or perceived risks of OC use. The RMP makes specific mention that it relates to YAZ and that its findings will also apply to the extended cycle regimen of YAZFlex. Breast cancer risk and venous thromboembolism receive particular attention. The RMP concludes with two commissioned external expert reports which are essentially rebuttals of the suggestion that there is a specific VTE risk associated with drospirenone as opposed to other progestogenic components of OCs.

Benefits

The data reviewed in this evaluation provide sound evidence of benefits to the user in terms of reduction in bleeding and other menstrual cycle associated symptoms. These benefits do not have a major impact on health but enhance the convenience and overall acceptability of the product to the user. Contraceptive efficacy is unimpaired. Efficacy in terms of control of acne is not likely to be altered. Whether efficacy in control of PMDD symptoms will be maintained with the extended cycle regimen has yet to be established.

Risks

No additional risks have been identified associated with the use of the extended cycle regimen. In particular, the possibility of a compromise to endometrial safety has been adequately excluded.

Balance

The benefit/risk equation for the use of the extended cycle regimen is favourable on the premise that less frequent menstruation is desired by the user; there is no adverse implication for the use of the standard monthly cycle regimen as an alternative approach.

Conclusions

YAZFlex is suitable for clinical use by women seeking oral contraception who prefer the extended cycle, 'managed bleeding' approach to menstrual cycle control.

Recommended conditions for registration

YAZFlex is suitable for registration provided that:

a. all aspects of safety monitoring continue as for the sponsor's existing registered product YAZ; and

b. the sponsor undertakes to provide evidence of efficacy in relation to the indication for treatment of premenstrual dysphoric disorder.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 13.

Table 13. Ongoing Safety Concerns

Important identified risks	Venous thromboembolism Arterial thromboembolism Breast cancer Benign and malignant liver tumors Disturbances of liver function Pancreatitis Increases in blood pressure Effect on hereditary angioedema
Important potential risks	Unrecognized pregnancy Cervical cancer Worsening of depression Crohns disease and ulcerative colitis Insulin resistance Hyperkalemia

	Unrecognized pregnancy
Important missing information	No important missing information associated with YAZ Flex has been identified

The above sponsor summary of the Ongoing Safety Concerns was considered acceptable by the TGA.

Pharmacovigilance plan

The sponsor has proposed to undertake a combination of routine[8] and additional pharmacovigilance activities for the ongoing safety concerns.

The sponsor was requested to provide additional information on additional pharmacovigilance activities to the TGA. The below sections on pharmacovigilance have been updated to reflect the additional information submitted by the sponsor as a result of this request. In addition, study information was also gathered from clinicaltrials.gov[1].

Additional pharmacovigilance activities

Monthly targeted ongoing monitoring

The aim of the targeted monthly ongoing monitoring report is to:

- Monitor the number and types of thromboembolic events from various sources;
- Provide information for review regarding reporting frequencies, outcomes and geographic distribution of events;
- Document the trends in reporting rates over time. For the purpose of the targeted monthly monitoring, sales data are used to estimate patient exposure.

Regular monitoring of reporting rates is expected to improve the interpretation of generated postmarketing safety data and support timely detection of potential safety signals.

Post authorisation safety studies

Table 14. Post authorisation safety studies

Post authorisation safety study	Assigned safety concerns		
	Identified	Potential	Study status
LASS[1]	ATE VTE Breast cancer Benign and malignant liver	Cervical cancer	Completed

[8]Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Post authorisation	Assigned safety concerns		
	tumours		
INAS[2]	ATE VTE Breast cancer Benign and malignant liver tumours	Cervical cancer	Ongoing
INAS-FOCUS[3]	ATE VTE Breast cancer Benign and malignant liver tumours	Cervical cancer	Ongoing

[1]LASS =Long-term Active Surveillance Study; [2]INAS= International Active Surveillance Study; [3]INAS-FOCUS= International Active Surveillance Study - Folate in Oral Contraceptives Utilization Study.

Long-term Active Surveillance Study for Oral Contraceptives (LASS)

Data from the European Active Surveillance Study cohort (EURAS), a prospective, controlled, non-interventional, active surveillance cohort (n=59,510 oral contraceptive (OC) users) with 1 to 5 years follow-up, suggested that DRSP containing OCs may have a lower risk of arterial thromboembolic events (that is, acute myocardial infarction and stroke). However, the EURAS study was not sufficiently powered to make this conclusion.

The Long-term Active Surveillance Study for Oral Contraceptives (LASS) was designed as an extension to EURAS with an additional 5 year follow-up period. LASS has now finished and the sponsor has provided a final study report to TGA.[9] This study consisted of three different groups of OCs: OCs containing DRSP (Yasmin), OCs containing levonorgestrel (LNG) and OCs containing other progestogens. Two further cohorts developed during the study as the OC users changed their contraceptive method to a non-hormonal method or stopped using hormonal contraception during the follow up period: no oral hormonal contraceptive (NOHC) and 'no-use' cohorts. Primary outcomes of interest were cardiovascular, specifically the incidence of arterial thromboembolic events (ATE) but also venous thromboembolic events (VTE) and cancer (n=58, 674 OC users).

No major differences were found between the cohorts in the rates for overall SAEs, organ-system specific SAEs, overall mortality and outcome-specific mortality, overall cancer and organ-system specific cancer. Overall, for all outcomes studied an increased risk in Yasmin users compared to users of other OCs (including LNG-containing OCs) was not identified. The study results were robust enough to show non-inferiority of Yasmin for venous thromboembolic events, while fewer arterial outcomes were identified in the Yasmin cohort. These results suggest that the risk of adverse cardiovascular outcomes for Yasmin use are not higher than the venous risks associated with the use of LNG containing OCs or other OCs, while the arterial risk appears to be lower.

[9]Sponsor comment: 'LASS is a prospective, controlled, non-interventional cohort study with two study arms: OCs containing drospirenone and OCs containing any other progestogen, in addition the study allowed to compare drospirenone-containing OCs to OCs containing levonorgestrel (LNG) as a subgroup of the Other OC cohort.'

International Active Surveillance Study (INAS) - Women taking oral contraceptives (INAS-OC)

INAS-oral contraceptives (OC) is a prospective, controlled, non-interventional cohort study with two study arms: OCs containing drospirenone and OCs containing any other progestogen. The study compares the short- and long-term risks of a 24 day regimen of a drospirenone (DRSP) containing oral contraceptive with the risks of established oral contraceptives in a study population that is representative of actual users. New users of an OC (starters, switchers without a pill intake break and recurrent users with a pill intake break [same or different OC]) are accrued by a network of prescribing physicians. The primary outcome is thromboembolic events. Baseline and 2 year follow-up information are collected via a self-administered questionnaire. Approximately 80, 000 participants will be recruited.

International active surveillance study – Folate and oral contraceptives utilisation study (INAS-FOCUS)

Also utilising INAS-OC study design, INAS-FOCUS has three study arms: users of oral contraceptives containing drospirenone, ethinyloestradiol and metafolin (DRSP/EE/metafolin), oral contraceptives containing dienogest, ethinyloestradiol and metafolin (DNG/EE/metafolin) and users of oral contraceptives containing other oestrogen/progestogen OC combinations. This study aims to compare the risks of short- and long-term use of these contraceptives. The primary outcomes are cardiovascular events and colorectal cancer, with follow-up data of 6 and 15 years, respectively, collected. Approximately 80, 000 women are expected to be enrolled. Baseline and follow-up information are collected via a self-administered questionnaire.

Unrecognised pregnancy and International Active Surveillance Study - Safety of Contraceptives: Role of Estrogens (INAS-like study for YAZFlex).

As an additional pharmacovigilance activity, for the potential risk unrecognised pregnancy, the sponsor has proposed to establish sentinel sites to capture information to assess if there is a delay in diagnosis of pregnancy resulting from the flexible cycle regimen and the decreased frequency of menses when using YAZFlex compared to selected short cycle COCs. The RMP provided very limited information on the establishment of the sentinel sites and the sponsor has provided additional information to TGA.[10]

The sponsor has agreed to investigate the question of delay in the diagnosis of pregnancy in the already planned large prospective active-surveillance study for YAZFlex. This study will be initiated with the launch of YAZFlex in Europe, since it is planned to recruit its participants from European countries. This INAS-like study for YAZFlex study will include approximately 50,000 women, representative of typical OC users. Based on experience with INAS-OC and other INAS-like studies, the 5 year follow-up of the 50,000 women should result in about 150,000 women years. Outcomes will be collected via questionnaire at baseline and follow-up visits.

The main clinical outcomes of interest will be cardiovascular outcomes, in particular venous thromboembolic events (VTE, primary variable), acute myocardial infarction, cerebrovascular events (ATE, secondary variable). However, an outcome of untended pregnancy will also be added to the existing standard questionnaire.[11] In addition, a further pregnancy related outcome of interest will be return to fertility.

[10] Sponsor comment: 'Bayer informed the TGA, that the sentinel site approach was abandoned due to feasibility issues and was replaced by the observational study approach.'
[11] Sponsor comment: 'Relevant data will be extracted both from user's questionnaire and her medical records. The question of delay in the diagnosis of pregnancy will be subject to validation process.'

OPR reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestones

Monthly targeted ongoing monitoring

The monthly targeting ongoing monitoring was considered acceptable.

Post authorisation safety studies

The design, outcome measures, follow-up duration and sample size of the post authorisation safety studies were considered acceptable for monitoring and further informing the assigned safety concerns.

Reporting milestones

The reporting milestones for the pharmacovigilance activities are considered acceptable. It is expected that study updates, including INAS-SCORE, will be provided via regular period safety update reports provided to the TGA.

Risk minimisation activities

Planned actions

Although the sponsor has stated they will not be undertaking any additional risk minimisation activities, they have stated that to address concerns that there may be 'off label' use of the product, that is, prescription of YAZ as acne treatment for women who do not seek hormonal contraception, if the proposed indications are approved, the sponsor is committed to conducting a risk minimisation program to ensure YAZ is prescribed and used according to its labelled indications.

The sponsor states that the proposed risk minimisation plan would consist of three elements:

- Two independently conducted drug utilisation studies:
    a. New drug utilisation study to monitor YAZ prescribing practices in Europe and the effectiveness of the educational outreach program
    b. Adaptation of the INAS study to monitor YAZ off label prescribing practices in Europe and to assess a potential public health risk due to YAZ off label use.
- An educational outreach program to reduce potential 'off label' use (only if prescribing rate for treatment of acne in women who are not seeking contraception is greater than 10%).

The sponsor believes that safety findings derived for conventional YAZ from this minimisation program will also apply for the extended-cycle regimen of YAZ.

OPR reviewer comment

The sponsor was requested to provide further information on these planned activities for potential off label use to the TGA. That is, whether these studies would be conducted in Australia or, if not, whether data collected in the EU would be able to be translated to the Australian context.

Unfortunately, the sponsor did not provide a response to this requested. The sponsor stated that the proposed indications for YAZFlex are the same as currently approved for YAZ. Furthermore, YAZ would not be appropriate for a woman with acne who does not elect to use oral contraception as per the approved indications and the same would apply for YAZFlex.

It is recommended that if this submission is approved that the sponsor provides, to the Office of Product Review (OPR), further information on these planned activities for the potential off label use of YAZ/ YAZFlex. This information may include but not be limited to;

if these activities are currently implemented in the EU, current synopses of these activities and whether this data is transferable to the Australian context. A date or milestone that these documents will be provided should be submitted.

Summary of OPR recommendations

The OPR provided these recommendations in the context that the submitted RMP is supportive to the application;

It was recommended to the Delegate that the sponsor:

1. Implement RMP Version 1, dated September 2010, including the sponsor's response to the TGA request for information/documents and any future updates be imposed as a condition of registration.
2. If this submission is approved, the sponsor should provide to the Office of Product of Review (OPR):
    a. An updated RMP to reflect the changes requested by the nonclinical evaluator in their report.
    b. Further information on the planned activities to address concerns that there may be off label use of YAZFlex in women with acne who do not elect to use oral contraception. This information may include but not be limited to; if these activities are currently implemented in the EU, current synopses of these activities and whether this data is transferable to the Australian context.
    c. A date or milestone that these documents will be provided should be submitted.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Product/dose form

The evaluator mentioned that YAZFlex *'is essentially a new presentation and dosing regimen of the sponsor's existing registered product YAZ, a fixed combination oral contraceptive (OC) in which active tablets are taken for 24 days and inactive (placebo) tablets for 4 days in each 28 day cycle. YAZFlex differs only in that the active tablets are taken for a longer and variable period of time from 24 up to 120 days, depending on when bleeding occurs, and that the inactive tablets are replaced by a 4-day tablet free interval, managed by interaction between the consumer and a dispensing device'*.

The letter of application states that YAZFlex tablets are contained in a plastic tube (a dispenser pack) and is inserted into a tablet dispenser. The tablet dispenser is reusable and is designed to fit a cartridge prefilled with YAZ active tablets. This dispenser assists the subject with, '*information on the current treatment cycle for the day, number of tablets remaining in the cartridge, whether the patient can take the 4-day tablet free interval...*'. During the 4 day tablet free interval the device will display the day of the tablet free break and when the active tablet is due.

There were no objections to approval of the oral contraceptive device and usability. The device evaluator recommended that a warning, 'keep out of the reach of children' be added on the device. The sponsor has stated that it does not wish to accept this recommendation as the risk of toxicity to the tablet is low; also the 'risk unauthorised use is low due to

physical and cognitive barriers to tablet access'. This was considered acceptable as there are adequate warning statements in the patient information leaflet and the carton.

All chemistry and quality control issues have been resolved.

Nonclinical

The evaluator comments that the new studies were of limited relevance. Previously submitted studies on continuous daily dosing supported this regimen.

Two new studies on pharmacology confirmed previous findings, that is, ethinyloestradiol possessed high affinity for oestrogen receptor (rat and human uterus), moderate affinity for progesterone receptor (rabbit and human uterus) and no androgenic receptor affinity. The second study demonstrated progestogenic activity of drospirenone in rats.

PK: A pharmacokinetic (single dose monkey) study showed no significant interaction between the active components. Pharmacokinetics of the active components have been established in previous submissions on Yasmin and YAZ.

Acute toxicity: A single dose toxicity study of ethinyloestradiol and drospirenone in combination (1:100 ratio) in rats showed a low order of toxicity, consistent with previously submitted data.

Repeat dose toxicity and Carcinogenicity studies: No new studies were submitted. Previously submitted data on continuous once daily dosing support this.

Reproductive toxicity: The evaluator discusses previously submitted data. A newly submitted study (EE±DRSP-1: 100 ratio as PO administration) revealed, 'embryolethality (increased post-implantation loss) but no teratogenicity at the highest dose in rats (0.1/10 mg/kg/day ethinyloestradiol/drospirenone PO), and an increased incidence of skeletal variations (principally wavy ribs) and retardation of ossification at ≥0.03/3 mg/kg/day'. These were at low multiples of clinical exposure. The evaluator recommends that YAZFlex be contraindicated in known or suspected pregnancy.

Several PI amendments were recommended by the nonclinical evaluator.

Clinical

Pharmacokinetics

The first is the population pharmacokinetic analysis from the pivotal efficacy Study A40196. This study compared the safety and efficacy of the YAZFlex regimen and a fixed extended regimen (YAZ Extend) to conventional YAZ regimen. This analysis showed that there was no significant difference in drug exposure between treatment groups. However, there was significant individual variation in exposure.

Clearance was shown to increase with body weight for both drug components.

Efficacy

Two pivotal studies (A40196 and A48294) are discussed by the clinical evaluator. Healthy women aged 18 to 35 years in A 40196 and 18 to 45 years in Study A48294 seeking contraception where COC use was not contraindicated were eligible to participate. There is also a supporting study, A47505.

Study A40196 was a multicentre, open, randomised parallel group study conducted in Europe and Canada comparing YAZFlex and YAZ Extend with conventional YAZ, for oral contraception. YAZ Extend is a regimen of one active tablet/day for 120 days followed by a 4 day tablet free interval to induce withdrawal bleeding.

Study A48294 was a multicentre open label study conducted in USA. Here, instead of YAZ Extend, YAZ Stop& Go was used in the third treatment arm. YAZ Stop & Go is similar to YAZFlex except that women are allowed to schedule their withdrawal bleeding at any time between Days 25 to 120 of the intake cycle according to convenience.

The primary efficacy endpoint in both studies was unintended pregnancy rate. Study A40196 also included total number of bleeding days as a co-primary endpoint.

Secondary efficacy endpoint in Study A48294 was bleeding pattern and cycle control.

Details of Pearl Index calculation, the assessment used to define bleeding patterns, sample size calculations and other study design details are discussed in the CER.

In Study A40196, the full analysis set (FAS) included 642 subjects in the YAZFlex group; 209 in the YAZ Extend group and 216 in the YAZ group. This was at 12 months.

In Study A48294 the FAS population as follows: 1406 in the YAZFlex group; 232 in YAZ Stop& Go; and 226 in YAZ group.

With respect to the demographic details (see Table 15 below), of note: Study A40196 included a lower body mass index (BMI) (22.6 kg/m2 versus 24.2 kg/m2); the population was also marginally younger (24.7 years versus 25.7 years). Study A48294 which was to include women up to the age of 45, included 13% of women above the age of 35 years in the YAZ Stop& Go and YAZ arms. It is not stated whether such women were recruited in the YAZFlex group. This should be stated in the sponsor's pre-Advisory Committee on Prescription Medicines (ACPM) response.

Table 15. Summary of Clinical Efficacy. Demographic details.

Table 3-6 Demographic parameters – FAS (pivotal studies A4019 and A648294)						
Study A40196 [a]	**YAZ Flex$_{MB}$ N = 642 (100%)**		**YAZ Extend N = 209 (100%)**		**YAZ N = 216 (100%)**	
Age, height, body weight, BMI (mean ± SD, range)						
Age (years)	24.8 ± 4.4	(18–35)	24.8 ± 4.5	(18–35)	24.3 ± 4.3	(18–35)
Height (cm)	167.2 ± 6.3	(150–187)	168.0 ± 6.2	(150–190)	167.8 ± 5.8	(155–187)
Body weight (kg)	63.1 ± 8.6	(46–93)	63.6 ± 8.8	(49–89)	63.4 ± 8.6	(46–91)
BMI (kg/m^2)	22.6 ± 2.7	(18–31)	22.5 ± 2.6	(18–30)	22.5 ± 2.8	(18–30)
Ethnic groups (number of women, %)						
Caucasian	636	(99.1%)	202	(96.7%)	212	(98.1%)
Black	0	–	1	(0.5%)	0	–
Hispanic	1	(0.2%)	0	–	0	–
Asian	3	(0.5%)	2	(1.0%)	2	(0.9%)
Other	2	(0.3%)	4	(1.9%)	2	(0.9%)
Educational level (number of women, %)						
Elementary	34	(5.3%)	10	(4.8%)	12	(5.6%)
Secondary	289	(45.0%)	80	(38.3%)	76	(35.2%)
College/university	319	(49.7%)	119	(56.9%)	128	(59.3%)
Current smoker (number of women, %)						
No	437	(68.1%)	142	(67.9%)	149	(69.0%)
Yes	205	(31.9%)	67	(32.1%)	67	(31.0%)
Alcohol consumption (number of women, %)						
Never	89	(13.9%)	27	(12.9%)	23	(10.6%)
Seldom	361	(56.2%)	99	(47.4%)	111	(51.4%)
Occasionally	166	(25.9%)	70	(33.5%)	65	(30.1%)
Regularly	26	(4.0%)	13	(6.2%)	17	(7.9%)
Study A48294	**YAZ Flex$_{MB}$ N = 1406 (100%)**		**YAZ Stop&Go N = 232 (100%)**		**YAZ N = 226 (100%)**	
Age, height, body weight, BMI (mean ± SD, range)						
Age (years)	25.2 ± 4.5	(18–35)	26.8 ± 6.8	(18–45)	27.3 ± 6.4	(18–45)
Height (cm)	[c]164.4 ± 6.9	(136–192)	165.4 ± 7.0	(150–185)	164.6 ± 6.3	(151–184)
[c] Body weight (kg)	65.3 ± 11.9	(16–166)	66.5 ± 12.6	(26–102)	65.7 ± 12.6	(20–99)
BMI (kg/m^2)	24.2 ± 3.9	(5.0–60.2)	24.3 ± 4.3	(10.8–34.4)	24.3 ± 4.4	(7.1–34.7)
Ethnic groups (number of women, %)						
Caucasian	1043	(74.2%)	179	(77.2%)	178	(78.8%)
Black	108	(7.7%)	22	(9.5%)	18	(8.0%)
Hispanic	197	(14.0%)	24	(10.3%)	23	(10.2%)
Asian	35	(2.5%)	0	–	1	(0.4%)
Other	23	(1.6%)	7	(3.0%)	6	(2.7%)
Educational level [b] (number of women, %)						
Elementary	7	(0.5%)	2	(0.9%)	1	(0.4%)
Secondary	249	(17.7%)	25	(10.8%)	32	(14.2%)
College/university	1149	(81.7%)	205	(88.4%)	193	(85.4%)
Current smoker [b] (number of women, %)						
No	1231	(87.6%)	203	(87.5%)	183	(81.0%)
Yes	174	(12.4%)	29	(12.5%)	43	(19.0%)
Alcohol consumption [b] (number of women, %)						
Never	282	(20.1%)	47	(20.3%)	49	(21.7%)
Seldom	432	(30.7%)	67	(28.9%)	48	(21.2%)
Occasionally	634	(45.1%)	96	(41.4%)	106	(46.9%)
Regularly	57	(4.1%)	22	(9.5%)	23	(10.2%)

[a] The above-data for study A40196 from the first year only; two-year data for YAZ Flex$_{MB}$ of study A40196 are available in the source table.
[b] Missing for 1 woman on YAZ Flex$_{MB}$ (study A48294)
[c] Erroneous weight for some women (for details, see database errata in module 5.3.5.1.A, A48294, section 16.1.9.2)

The following table (Table 16) gives the Pearl Indices.

Table 16. Pearl Indices based on pregnancies during treatment-FAS (pivotal studies A40196 and A48294)

	YAZ Flex$_{MB}$ EU/Canada study A40196	YAZ Flex$_{MB}$ US study A48294	YAZ Flex$_{MB}$/YAZ Stop&Go pooled [a] data from A40196 and A48294
All women			
Number of women	888	1406	2526
Total time of exposure (wy)	1275.45	1081.01	2545.14
Cycles with backup contraception (wy)	16.85	66.15	104.38
Relevant exposure time (wy) for PI	1268.16	1032.48	2470.85
Number of pregnancies for PI	8	17	31
PI	**0.63**	**1.65**	**1.25**
Upper 2-sided 95% confidence limit of PI	1.24	2.64	1.78
Relevant exposure time (wy) for PI$_A$	1179.06	833.41	2154.61
Number of pregnancies for PI$_A$	7	14	27
PI$_A$	**0.59**	**1.68**	**1.25**
Upper 2-sided 95% confidence limit of PI$_A$	1.22	2.82	1.82
Women between 18 and 35 years of age			
Number of women	888	1406	2496
Total time of exposure (wy)	1275.45	1081.01	2521.01
Cycles with backup contraception (wy)	16.85	66.15	102.31
Relevant exposure time (wy) for PI	1268.16	1032.48	2448.34
Number of pregnancies for PI	8	17	31
PI	**0.63**	**1.65**	**1.27**
Upper 2-sided 95% confidence limit of PI	1.24	2.64	1.80
Relevant exposure time (wy) for PI$_A$	1179.06	833.41	2134.9
Number of pregnancies for PI$_A$	7	14	27
PI$_A$	**0.59**	**1.68**	**1.26**
Upper 2-sided 95% confidence limit of PI$_A$	1.22	2.82	1.84

Abbreviations: wy = women years, PI = Pearl Index, PI$_A$ = adjusted PI (see section 3.2.1.A for definition).
One woman year is defined as 364 days.

[a] YAZ Flex$_{MB}$ data from studies A40196 and A48294, YAZ Stop&Go data from study A48294 only.
The PI and upper 95% confidence limit for YAZ Flex$_{MB}$ presented in the study reports (module 5.3.5.1.A, A40196, section 8.3.1 and module 5.3.5.1.A, A48294, section 8.3.1) are similar but not identical to the above (integrated analysis). There are minimal differences in the calculated relevant exposure time because different approaches had been taken in the calculation of time on backup contraception.

Note: The PI calculations include 4 women (PID nos. 3797 and 4528 from the EU/Canada study; PID nos. 33001 and 50030 from the US study) who had taken concomitant medication (e.g. antibiotics) that could interfere with the efficacy of the study medication. Three women (PID nos. 38009, 41023, and 87028), conservatively assessed as 'method failures' for having failed to use backup contraception effectively, could be considered as 'subject failures' with 0 days of valid exposure. Details concerning each of these women are provided in the individual case narratives in the clinical study reports (module 5.3.5.1.A, A40196, section 14 and 5.3.5.1.A, A48294, section 14.3).

The difference in Pearl Index in the two studies is attributed to lower compliance in US. This was dismissed by the evaluator (see above).

The life table analysis is as described in Table 17 below.

Table 17. Summary of Kaplan Meier estimates and confidence intervals for one year of treatment by study; FAS (Studies A40196 and A48294).

	Kaplan Meier estimator	95% confidence limit Upper	95% confidence limit Lower	Probability of no conception
All women				
YAZ Flex$_{MB}$ (study A40196)	0.0142	0.9709	0.9931	98.58%
YAZ Flex$_{MB}$ (study A48294)	0.0163	0.9737	0.9899	98.37%
YAZ Flex$_{MB}$/YAZ Stop&Go [a]	0.0222	0.9649	0.9860	97.78%
Women between 18 and 35 years of age				
YAZ Flex$_{MB}$ (study A40196)	0.0142	0.9709	0.9931	98.58%
YAZ Flex$_{MB}$ (study A48294)	0.0163	0.9737	0.9899	98.37%
YAZ Flex$_{MB}$/YAZ Stop&Go [a]	0.0224	0.9647	0.9858	97.76%

[a] YAZ Flex$_{MB}$ data from studies A40196 and A48294, YAZ Stop&Go data from study A48294.

Bleeding patterns are discussed under *Clinical Findings* above.

The evaluator noted that in Study A40196:

- YAZFlex subjects had an average of 62% as many bleeding days as YAZ subjects.

- YAZFlex subjects had less bleeding days: average 41 compared with 61 days for YAZ Extend.
- The mean length for withdrawal bleeding was:

Group A (YAZFlex)	7.5 to 9.8 days
Group B (YAZ Extend)	9.8 to 10.5 days
Group C (YAZ)	4.4 to 5.2 days

The evaluator mentions that these studies show that women using YAZFlex had significantly less bleeding days, less frequent episodes of bleeding but longer periods of withdrawal bleeding than women using the standard cyclical preparation YAZ.

The supportive Study A47505 that evaluated the symptomatology relating to dysmenorrhoea included 115 subjects in the YAZFlex arm and 108 subjects in the YAZ arm. The data on the number of bleeding days and frequency of bleeding were similar to those of the pivotal studies.

Safety

The evaluator mentions that 2409 women were exposed to YAZFlex. The common adverse events are not discussed.

There were three confirmed VTE reports in YAZFlex group in Study A40196. In Study A48294 there were two further cases of suspected DVT. The evaluator calculates the incidence of VTE episodes as either 1.2 or 1.6/1000 WY. The evaluator concludes that this is consistent with the general experience with DRSP/EE preparation.

There was one episode of breast cancer in Study A40196.

Laboratory findings were in line with expectations.

Overall recommendation by the clinical evaluator

Overall, the evaluator is of the opinion that efficacy results were equivalent to YAZ in terms of contraception. In terms of cycle control and bleeding YAZFlex was superior in reducing the number of bleeding days and improving user satisfaction. Overall, no safety concerns were identified by the evaluator to preclude registration.

Risk management plan

Of note, the evaluator discusses the risk of venous and arterial thrombo-embolism and the post market studies, European Active Surveillance Study (EURAS) and its five year extension, Long Acting Surveillance study (LASS) which support the claim that drospirenone does not have an increased risk of venous and arterial thrombo-embolism compared with levonorgestrel.

Overall, the evaluator is satisfied with the routine pharmacovigilance activities and the regular updates of post authorisation safety studies proposed in the RMP.

The Committee should note that an advisory committee of the FDA convened on the 8 December 2011 to review and discuss the overall risk benefit profile of oral contraceptive pills (OCPs) containing DRSP. This is because the FDA had conducted a large retrospective cohort study to evaluate the risk of venous or arterial thrombo-embolic events or death. The outcome of this meeting should be provided in the sponsor's pre Advisory Committee on Prescription Medicines (ACPM) response.

Risk-benefit analysis

Three TGA Delegates provided risk-benefit analyses on three different aspects of this application. The Delegate's Overview included above was written by Delegate 1.

The indications

Treatment of moderate acne vulgaris in women who seek oral contraception and Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraceptives as their method of birth control

are the responsibility of other clinical evaluation units at the TGA. The mechanism of action in these indications is not the same as that which is the direct effect of ovarian suppression and effects on cervical mucus that pertains with the oral contraceptive indication.

The recommendations by the Delegates relating to these indications are included below as *Delegate 2* and *Delegate 3 Considerations*.

Delegate 1 considerations

Efficacy for oral contraception is shown in this data set with the YAZFlex regimen. This regimen is advantageous due to its claims regarding withdrawal bleeding and is likely to be used by females who are younger than 18 years; however data are only submitted in those over the age of 18 years. In this context, the ACPM is asked to note and comment the following:

1. The effect on bone mineral density (BMD) in the younger age group of women who would take YAZFlex over a long period of time is not known. For example, they may miss attaining peak BMD. (The evaluator mentions a subgroup of subjects in pivotal Study A40196 who had BMD measurements, however, this was not undertaken in the YAZFlex group). The suitability in women under 18 years of age is not known in regard to this safety issue.
2. Return to ovulation and fertility has not been assessed in this data set. It cannot be assumed to be equivalent to YAZ, so what women might be told is unclear.
3. Older women who would take combined oral contraceptives are more likely to have thrombo-embolic episodes. Also, there may be specific risks associated with this particular progestogen. Adequate data on this were not submitted. The second study, which included women up to the age of 45, might have information on this subgroup who were treated with YAZFlex. The sponsor should submit a summary of the adverse event profile for this sub group in their pre-ACPM response.

All PI recommendations made by the evaluator should be adopted by the sponsor.

Delegate 1 proposed to approve YAZFlex for oral contraception.

The Committee's advice was sought on all proposed recommendations.

Delegate 2 considerations

Consideration of the proposed indication: 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 treatment of PMS (premenstrual syndrome), See CLINICAL TRIALS.

The purpose of this submission is to register a new dose regimen for an existing fixed combination oral contraceptive. The above indication was approved for YAZ when it was registered in February 2008. Prior to registration the Australian Drug Evaluation Committee (ADEC; the predecessor of the ACPM), considered evidence to support the

above indication for the current dose regimen for YAZ, that is, one active tablet taken once daily for 24 days followed by a placebo tablet taken once daily for 4 days with the cycle continuing indefinitely. The Delegate noted that the *Dose Recommendations* for YAZ also provide information on how to delay a period however this advice does not extend to the dose regimen that has been proposed with this submission.

At the time of approval of the current indication pertaining to Premenstrual Dysphoric Disorder (PMDD) the TGA had provided no guidance on the development of medicines for the treatment of symptoms of PMDD. On 14 April 2009 the TGA published on its website an European Medicines Agency (EMA) Concept Paper on the need for a guideline on the treatment of PMDD. That paper was provided for information only. The EMA has now developed a guidance document which comes into effect within the EMA from February 2012. It is likely the TGA will seek to adopt this guideline in due course. While not currently adopted by the TGA [at the time of this Overview], this guideline nevertheless contains important guidance concerning the assessment of PMDD, including the recommended duration of assessment for efficacy and safety.

Of particular note the guideline provides the following information and recommendations:

- The document is intended to provide information on the identification of the target population including special populations (adolescents), study duration, efficacy and safety endpoints to establish efficacy and safety in PMDD.
- Due to the chronic nature of the disorder special attention should be paid to maintenance of effect and long-term safety, and the presence and acceptance of co morbidity.
- Given the chronicity and cyclicity of the symptoms, the maintenance of therapeutic efficacy should be demonstrated over at least 6 cycles. Since PMDD is a chronic condition, clinical studies should be long enough to provide information about effectiveness, tolerability and patient compliance. In order to establish efficacy, placebo-controlled data are needed over at least 6 cycles (2 run-in cycles ± 6 treatment cycles), especially since a large placebo effect is expected.
- There is a need to demonstrate that specific therapeutic strategies have similar beneficial effects in adolescents and it is requested to include adolescents in the development program according to the prevalence in the general population.
- When pharmacological treatment is stopped, rebound and/or withdrawal phenomena may occur. Therefore, rebound and/or withdrawal phenomena should be systematically investigated.
- Since PMDD is a chronic disorder expected to last until menopause, long-term safety of therapeutic interventions has to be established. The total clinical experience should generally include data on a large and representative group of patients in line with the guideline on population exposure (ICH E1[12]). Depending on the mode of action of the examined treatment special attention should be paid to long-term effects on endocrinium. Intermittent versus continuous treatment strategies might have different impacts on long-term adverse events.

The current submission contains no new data on efficacy or safety of YAZ in the treatment of PMDD. The proposed dose regimen has not been examined in women with PMDD. An assumption has been made by the sponsor that data on efficacy and safety of YAZ in the treatment of PMDD could be extrapolated to the new dose regimen.

Delegate 2 did not accept that this extrapolation was warranted. Delegate 2 considered that:

[12]ICH E1: The Extent of Population Exposure to Assess Clinical Safety /III/5084/94, CPMP/ICH/375/95

- symptoms of PMDD may be different with a prolonged cycle of exposure to the components of YAZ, that is, either more or less severe;
- that efficacy with use of the proposed new dose regimen may be different from efficacy of YAZ given in a 28 day cycle;
- there has been no assessment of whether efficacy would be maintained; and that
- rebound and/or withdrawal effects in women with PMDD given the proposed dose regimen have not been examined.

Delegate 2 was concerned that long term effects on the endocrinium from the proposed new dose regimen have not been assessed. This safety concern applies to all indications proposed for this new dose regimen for YAZ.

Conclusion and recommendation by Delegate 2

Delegate 2 proposed to reject the indication of:

> *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 treatment of PMS (premenstrual syndrome), See CLINICAL TRIALS for YAZ.*

If other indications are approved the PI should include a statement that efficacy and safety of YAZFlex has not been assessed for:

> *Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraceptives as their method of birth control. YAZFlex is not recommended for treatment of PMDD.*

The general advice of the ACPM was requested.

Delegate 3 considerations

Consideration of the proposed indication: Treatment of moderate acne vulgaris in women seeking oral contraception.

This indication is currently approved for the standard YAZ dosing regimen. No new efficacy data were included in the application for YAZFlex.

The clinical evaluator has discussed the proposed acne indication for YAZFlex in the clinical evaluation report. The evaluator considered that suppression of ovarian hormone production, including androgen production, would be maintained throughout the extended treatment cycle of YAZFlex and that therefore efficacy in acne is likely to be maintained.

The submission contained some data on testosterone suppression in a subgroup of subjects in Study A40196 (308683). Treatment with either YAZ or YAZFlex was associated with approximately a 50% reduction in serum testosterone levels which was maintained out to 1 year. The evaluator therefore concluded that YAZFlex is likely to be as effective as YAZ for the control of moderate acne.

The safety data from the submitted studies did not raise any concerns that would preclude approval for use in oral contraception, and therefore safety will be acceptable in patients with moderate acne who seek oral contraception.

Delegate 3 proposed to approve the application. The advice of the Committee was requested.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of pharmaceutical efficacy, safety and quality considered this product to have a positive benefit-risk profile for the indication:

YAZFlex is indicated for:

1. *Oral contraception*
2. *Treatment of moderate acne vulgaris in women who seek oral contraception.*

In considering this application, the ACPM advised that the absence of efficacy data to support the broader indication for premenstrual dysphoric disorder (PMDD) precludes the incorporation of this condition in the indications. The ACPM noted the imminence of guidelines on PMDD and clarification of diagnostic status in the near future and recommends the sponsor provide suitable data to support efficacy claims.

The ACPM supported the amendments proposed by the Delegate to the Product Information (PI) and Consumer Medicines Information (CMI).

Specific conditions of registration which may be considered include the submission of further evidence to support PMDD indication. Longer term (>3 cycles) data for YAZFlex should be submitted.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Bayer withdrew their application for the Indication:

> *'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 3 months. YAZ has not been evaluated for treatment of PMS (premenstrual syndrome), See CLINICAL TRIALS'.*

Based on a review of quality, safety and efficacy, TGA approved the registration of YAZFlex ethinyloestradiol (as betadex clathrate) 20 µg, drospirenone 3 mg tablet dispenser pack for oral administration, indicated for:

YAZFlex is indicated for use as:

1. *an oral contraceptive*
2. *treatment of moderate acne vulgaris in women who seek oral contraception.*

Specific conditions applying to these therapeutic goods

1. The implementation in Australia of the YAZFlex ethinyloestradiol (as betadex clathrate) 20 µg, drospirenone 3 mg tablet dispenser pack Risk Management Plan (RMP) version Implement RMP Version 1, dated September 2010, included with this submission, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The Product Information current at the time this AusPAR was published is at Attachment 1. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au