28 September 2012
EMA/552336/2012
Patient Health Protection

Assessment report for Yvidually and associated names

Pursuant to Article 29(4) of Directive 2001/83/EC

International Non-proprietary Name of the active substance: ethinylestradiol and drospirenone

Procedure no: EMEA/H/A-29/1330

Referral under Article 29(4) of Directive 2001/83/EC

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion during the referral procedure

1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Bayer B.V submitted an application for decentralised procedure of Yvidually and associated names, 0.02 mg/3 mg film-coated tablets on 3 November 2010 that started on 6 December 2010 (NL/H/2041/001/DC).

The application was submitted to the reference Member State (RMS) : the Netherlands and the concerned Member States (CMS) : Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, Malta, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia and the United Kingdom.

On day 210, France had major issues on the efficacy of the product, which remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended, by the Netherlands on 25 December 2011. The CMD(h) 60 day procedure was initiated on 26 December 2011.

Day 60 of the CMD(h) procedure was on 23 February 2012 and since there was no agreement, the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC as amended, to the CHMP was made by the Netherlands on 23 February 2012. France raised public health objections regarding the contraceptive efficacy of the proposed dosing scheme, the bleeding pattern of the dosing regimen and the tablet dispenser which is regarded to have been insufficiently studied for Yvidually and associated names.

2. Scientific discussion during the referral procedure

2.1. Introduction

The current application concerns Yvidually and associated names for the indication of oral contraception. Yvidually extended dose regimen has been developed based on the marketed combined oral contraceptive YAZ 24+4 for women who want to postpone the withdrawal bleeding by extending the intake cycle up to 120 days. Each film-coated tablet of Yvidually contains 3 mg of drospirenone (DRSP) + 20 micrograms of ethinylestradiol (EE). Yvidually is intended to be marketed with an innovative tablet dispenser with a reminder function. The composition of Yvidually is identical to the authorised combined oral contraceptive YAZ 24+4.

Although common in the US, at present, no extended use combined oral contraceptive (COC) is approved in the EU; all COCs marketed in Europe employ a cyclic dose regimen of 21 or 24 days of hormone intake followed by a 4 to 7 day hormone-free interval.

The Marketing Authorisation Application included two pivotal Phase III studies;

- EU/Canada study – Study A40196, where the patients are from centers in the EU and Canada. This was open-label, randomized, active-controlled, parallel-group study, followed by 1 year uncontrolled extension of the YAZ FlexMB regimen.

- US study – Study A48294 where the patients are from study centers in the US. This was a open-label, randomized, active-controlled, parallel-group study

These two studies were conducted between 2005 and 2009, and have investigated the contraceptive efficacy (i.e. the number of unintended pregnancies, Pearl Index (PI) and cumulative pregnancy rate), as well as the bleeding pattern and cycle control parameters.

An interim analysis of an additional ongoing European multi-centre randomised open study 14701 (cut off date January 2012) has also been submitted.

Although the product is based on YAZ 24+4, this application was submitted according to Article 8(3) of Directive 2001/83/EC - full application, and assessed according to the decentralised procedure, with the Netherlands acting as RMS (NL/H/2041/001/DC). Since no agreement was reached during the CMDh referral, the procedure was referred to the CHMP according to Article 29(4).

2.2. Critical evaluation

Contraceptive efficacy of the dosing regimen

Dose recommendations

With the regimen applied for, a tablet-free interval is allowed at any time during day 25 to 120 of the treatment cycle – i.e. any 4-day break can only be started if tablet taking has been continuous for 24 days. After each 4-day tablet-free interval, a new mandatory intake cycle of a minimum of 24 days starts.

The dose recommendation consists of two phases:

1. Mandatory phase (Day 1 to day 24):

When starting intake of Yvidually, tablets must be taken continuously for a minimum of 24 days

2. Flexible phase (Day 25 to Day 120)

During days 25-120, the tablets can be taken continuously up to a maximum of 120 days. Within this period, the woman may decide herself to take a 4-day tablet-free interval or not. This means that 3 options are possible:

- During days 25-120, the woman can decide to take tablets continuously up to a maximum of 120 days. She schedules no withdrawal bleeding, thus no tablet-free interval.

Or:

- During days 25- 120, she may schedule a 4-day tablet-free interval (induction of withdrawal bleeding) in the event of 3 consecutive days of bleeding.

Or:

- During days 25- 120, the woman may decide to take a 4-day tablet-free interval (she schedules a withdrawal bleeding) at any time that suits her best, and irrespective of bleeding.

General dosing rules:

- Any 4-day tablet free interval can only be started if tablet taking has been continuous for 24 days i.e. after the completion of the mandatory phase.
- After any 4-day tablet-free interval, a new mandatory phase starts, i.e. tablets must be taken for a minimum of 24 days before any new break can be scheduled.

Clinical studies

The 2 phase III studies were conducted from 2005 to 2009 (study A40196 in Europe and Canada and study A48294 in the US). Both were presented as pivotal studies with regard to the efficacy and safety assessment of Yvidually.

These studies evaluated contraceptive efficacy, i.e. the number of unintended pregnancies, PI (calculated as the pregnancy rate in population divided by 100 years of user exposure) and cumulative pregnancy rate in the YAZ Flex MB arms, as well as bleeding pattern and cycle control parameters in all treatment arms of both studies.

Additionally, a third study (A47505) was conducted in women with moderate to severe primary dysmenorrhea and is presented as a supportive clinical trial regarding information on bleeding pattern during use of the extended dose regimen. This study A47505 was not assessed as in this study YAZ $Flex_{MB}$ was intended for the treatment of dysmenorrhoea instead of contraceptive efficacy.

An overview of the three studies is given in Table 1-1.

Table 1-1 Clinical development program: overview of clinical studies to evaluate the efficacy of YAZ Flex

Study no. (Protocol no.) Phase Location	Design Duration	Number of women treated (full analysis set)		Study objectives
Pivotal efficacy studies				
A40196 (308683) Phase 3 Germany [c], Canada, The Netherlands	Multicenter, open-label, randomized, parallel-group study Approximately 1 year, followed by 1 year safety extension with YAZ $Flex_{MB}$ only	YAZ $Flex_{MB}$: YAZ Extend: YAZ:	888[a] 209[b] 216[b]	To evaluate the safety and efficacy of YAZ in two variations of an extended regimen (YAZ $Flex_{MB}$ and YAZ Extend), compared to the conventional YAZ regimen administered in healthy women between 18 and 35 years of age, requesting contraceptive protection
A48294 (311642) Phase 3 United States	Multicenter, open-label, 3-arm, active-controlled study 1 year	YAZ $Flex_{MB}$: YAZ Stop&Go: YAZ:	1406 232 226	To evaluate the efficacy and safety of YAZ in a flexible variation of an extended regimen (YAZ $Flex_{MB}$), and to compare the effects on vaginal bleeding and safety with another flexible variation of an extended regimen (YAZ Stop&Go) and the conventional YAZ regimen administered in healthy women between 18 and 45 years of age, requesting contraceptive protection.
Supportive YAZ Flex study				
A47505 (310882) Phase 3 Germany	Multicenter, open-label, randomized, controlled, parallel-group study 5 cycles, each cycle comprising 28 days, resulting in 140 days of consecutive intake	YAZ $Flex_{MB}$: YAZ:	115 108	To evaluate the safety and efficacy of YAZ in a conventional and extended flexible regimen in the treatment of moderate to severe primary dysmenorrhea.

[a] This includes women treated with YAZ $Flex_{MB}$ during the first and/or second year, and women who switched from previous YAZ Extend or YAZ treatment to YAZ $Flex_{MB}$ after the first year. A total of 642 women were treated with YAZ $Flex_{MB}$ in the first year (module 2.7.3.A).

[b] In general, these women were treated for only one year with YAZ Extend or YAZ, except for 7 women in the YAZ Extend group and 21 women in the YAZ group who continued with their previous treatment during the second year for the assessment of BMD and bone markers.

[c] Note that 67 women from one study center in Germany (Krumbach), that was suspected of misconduct, were excluded from the full analysis set (FAS, 42 women on YAZ $Flex_{MB}$, 12 women on YAZ Extend, 13 women on YAZ) and hence, from all efficacy and safety analyses.

The following dose regimens were studied in the two pivotal 3-armed clinical Phase III studies:

- **YAZ Flex Managed Bleeding (YAZ $Flex_{MB}$) regimen**; each cycle comprises 120 days of intended treatment followed by a 4-day tablet-free interval to induce withdrawal bleeding. If 3 consecutive days of bleeding and/or spotting occurred during a treatment cycle, a 4-day tablet-free period was advised (i.e. 'managed bleeding' = MB). This treatment arm was included in both EU/Canada study and the US study and considered to be representative for the contraceptive efficacy of Yvidually, as well as a comparison of the bleeding pattern with the bleeding pattern of YAZ 24+4 and other dose regimens;
- **YAZ Stop & Go regimen;** each cycle comprises 120 days of intended treatment followed by a 4-day tablet-free interval to induce withdrawal bleeding. Irrespective of bleeding and/or spotting, women are allowed to schedule their withdrawal bleeding (i.e. the 4-day tablet-free interval) at

any time between days 25 and 120 of the treatment cycle. But women had also the option to follow the bleeding rules of the YAZ $Flex_{MB}$. This arm was included in the US study for comparison of bleeding pattern with bleeding patterns of YAZ 24+4 and YAZ $Flex_{MB}$;

- **YAZ fixed extended regimen**; 120 days of continuous tablet-taking (without any break) followed by a 4-day tablet-free interval. This arm was included in the EU/Canada study in order to compare with bleeding patterns of the other treatment arms;
- **YAZ 24+4 (YAZ) regimen**; 24 days of continuous tablet-taking followed by a 4-day tablet-free interval (regimen authorised in Europe) included in both studies in order to compare bleeding patterns;

Except for the YAZ fixed extended regimen, the minimum treatment period between tablet-free intervals (i.e. minimum cycle length) in each regimen was 24 days (to maintain contraceptive efficacy).

Table 1 Overview of the different regimens studied in the pivotal trials

US study A48294 (3 arms)	EU/CAN study A40196 (3 arms)
YAZ Flex MB in **1400** women for 1 year (**contraceptive efficacy + bleeding**)	YAZ flex MB in **880** women for 2 years (**contraceptive efficacy + bleeding**)
YAZ Stop & Go in **200** women for 1 year (**bleeding**)	YAZ fixed extended in **200** women for 1 year (**bleeding**)
YAZ 24+4 in **200** women for 1 year (**bleeding**)	YAZ 24+4 in **200** women for 1 year (**bleeding**)

Contraceptive efficacy

The contraceptive efficacy was investigated in the YAZ Flex MB regimen arm in both pivotal studies. The YAZ Stop & Go arm (in the US study only), the YAZ fixed extended arm (in the EU/Canada study) and the YAZ 24+4 arm (both studies) were included in the two studies to compare different bleeding patterns. The Pearl Index (PI) calculated as the pregnancy rate in the study population divided by 100 years of user exposure, was used to assess contraceptive efficacy.

- YAZ Flex MB regimen

The contraceptive efficacy was demonstrated for the YAZ Flex MB regimen in the pivotal EU/Canada study A40196, by a PI of 0.63 with a corresponding upper limit of the 95% confidence interval of 1.24 in women between 18 and 35 years of age, and a PI for method failure (PI_A adjusted) of 0.59 (upper limit 95% confidence interval 1.22), as shown in the table below. In this study, Pearl Indices obtained were in line with those obtained in the original file of YAZ 24+4. As the difference between the point estimate and the upper limit of the 95% CI is smaller than 1, it can be concluded that this EU-Canada study on its own is sufficiently large with regard to requirements on precision of the point estimate as recommended in the CHMP Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CPMP/EWP/519/98 (Rev 1), and therefore considered reliable.

Also noted in the table below, higher PIs were obtained in the other pivotal study A48294 that was carried out in the US. Higher PIs have also been observed for other COCs in studies performed in the US, which is probably related to problems with compliance.

Thus, the CHMP only considered the EU-Canada study, which is the study that included women in Europe (n=880) as pivotal for the assessment of the contraceptive efficacy of Yvidually.

Main contraceptive efficacy results obtained in the pivotal trials in the YAZ FlexMB arms

Table 3-19 Pearl Indices (PI) based on pregnancies during treatment – FAS (pivotal studies A40196 and A48294)

	YAZ $Flex_{MB}$		YAZ $Flex_{MB}$/YAZ Stop&Go
	EU/Canada study A40196	US study A48294	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).

- YAZ Stop & Go regimen

The YAZ Stop & Go arm (in the US study only), the YAZ fixed extended arm (in the EU/Canada study) and the YAZ 24+4 arm (in both studies) were included in the two studies to compare different bleeding patterns, but were not powered to assess contraceptive efficacy. Notwithstanding, during the initial DCP procedure a calculation of the PI was requested for the Stop & Go arm, YAZ fixed extended arm, and YAZ 24+4 arm, see table below:

Table 2 Pearl index in the treatment arms YAZ Stop & Go, YAZ fixed extended and YAZ 24+4

	YAZ Stop and Go	YAZ fixed Extended	YAZ 24+4	
	US study A48294	EU/Canada study A40196	EU/Canada study A40196	US study A48294
Pearl Index	**3.52**	0.00	1.07	1.20
95% CI	1.29 - 7.67	0.00 – 3.47	0.13 – 3.85	0.15 – 4.35

When looking at the results of the YAZ Stop and Go regimen, it was noted that the PI was higher (3.52; 95% CI; 1.29 - 7.67) compared to the YAZ Flex MB regimen in the same study (1.67 95% CI; upper limit 2.67). However it was discussed and noted that the high PI in YAZ Stop & Go arm of US-study A48294 was based on only 170 Woman Years (WY) of use, resulting in a wide 95% CI; 3.52 (95% CIs: 1.29 - 7.67). This high PI outcome is unreliable and not in line with CHMP Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CPMP/EWP/519/98 Rev 1), which requires that a sufficient number of cycles should be studied to obtain the desired precision of the estimate of contraceptive efficacy. The key studies should be at least large enough to give the overall PI (number of pregnancies per 100 woman years) with a two-sided 95% confidence interval such that the difference between the upper limit of the 95% confidence interval and the point estimate does not exceed 1. In addition, the number of patients in this YAZ Stop & Go arm is much lower compared to the Flex MB regimen (200 vs. 1400 patients) hampering any comparison. Also, as already stated earlier, the US population is not considered representative of the EU population.

Additionally, as presented by the applicant, only slight differences in the number of cycles (i.e 4-day breaks) and mean cycle length (number of days of continuous intake of tablets) between YAZ Flex MB variant and the YAZ Stop & Go regimen were observed (see tables below).

Table 1: Number of Cycles (Full Analysis Set) – US Study (A48294)

Treatment	no. of subjects	Mean	SD	Min	Q1	Median	Q3	Max
YAZ Flex MB	1317	4.2	2.2	1	3.0	4.0	5.0	13
YAZ S&G	222	4.6	2.5	1	3.0	4.0	6.0	14
YAZ 24+4	207	10.1	4.4	1	6.0	13.0	13.0	15

Source: Table 129 from CSR A48294 – Table 8-19 - Page 97

Table 2: Cycle length – US Study (A48294) and EU Study (A40196) - FAS

Note: The last cycle			YAZ Flex MB A48294	YAZ Flex MB A40196	YAZ Extended A40196	YAZ Stop&Go A48294
	Cycle length (days)	n	4258	2214	368	799
		Mean	73	78.2	121.5	70.4
		SD	40	39.8	27.9	38.7

It is not expected that these slight differences in mean number of cycles (4.2 versus 4.6 breaks/year) and cycle length (73-78.2 versus 70.4 days of continuous tablet intake per treatment cycle) between YAZ Flex MB and YAZ Stop & Go will lead to a relevant difference in contraceptive efficacy. In general, the reason for the break (bleeding occurrence or woman's own choice) will not influence the contraceptive efficacy, as long as the general rules of intake will be adhered to, that is regular uninterrupted daily tablet intake for at least 24 days and tablet-free intervals of a maximum of 4 days between intake cycles. Moreover, with considerably less 4-day tablet-free intervals and longer periods of active treatment in both variants, it is highly likely that the efficacy will be at least as good as established for YAZ 24+4. In the conventional YAZ 24+4 arm, the number of 4-day tablet-free intervals within one year is 10.1, as the tablet-free intervals are mandatory (i.e. 24 days of tablet intake followed by a 4 day break (YAZ 24+4)), versus 4.2 and 4.6 breaks for YAZ Flex MB and YAZ Stop & Go respectively, see table 1. Based on the above considerations, it was concluded that contraceptive efficacy had been sufficiently demonstrated with the YAZ Flex MB variant of the regimen (Pearl Index of 0.63, upper limit of 95% CI 1.24), which is considered representative of the proposed dosing regimen of Yvidually with regard to contraceptive efficacy.

- Interim analysis of the European study 14701

Further evidence for the efficacy of the YAZ Stop & Go regimen was obtained when the results of an interim analysis of an additional ongoing European multi-center randomised open study 14701, using the dispenser with the proposed dosing regimen of Yvidually became available. The exposure was limited to 357 women-years (wy), but the calculated PI was 0, with an upper limit of the 95% confidence interval of 1.0 fulfilling the requirements of precision of the CHMP Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CPMP/EWP/519/98 Rev 1). Although the final results will only be available in 2013, this PI is considered conclusive in terms of precision.

In summary, Yvidually has been developed for women who want to postpone the monthly withdrawal bleeding, occurring with the marketed combined oral contraceptive YAZ 24+4, by extending the intake cycle up to 120 days. It is concluded that contraceptive efficacy of Yvidually has been sufficiently

demonstrated for the proposed dosing regimen of Yvidually that allows the woman to decide herself to take a 4-day tablet-free interval or not during the flexible phase.

Evidence is primarily based on the adequate pearl indices obtained on EU/Canada study including an European population that allowed a 4-day tablet-free interval in case of 3 consecutive days of bleeding and/or spotting (Flex MB regimen). The reason for the break (bleeding occurrence or woman's own choice) will not influence the contraceptive efficacy, as long as the general rules of intake will be adhered to, that is regular uninterrupted daily tablet intake for at least 24 days and tablet-free intervals of a maximum of 4 days between intake cycles. No significant differences in number of cycles and mean cycle length were observed when a 4-day tablet-free interval was allowed irrespective of bleeding and/or spotting (Stop & Go regimen). Moreover, with considerably less tablet-free intervals and longer periods of active treatment in both variants, efficacy will be at least as good as established for the currently authorised YAZ 24+4. Based on the above, the CHMP agreed that the results of the YAZ Flex MB regimen could be extrapolated to a regimen where women are allowed to schedule their withdrawal bleeding irrespective of bleeding and/or spotting. Further supportive evidence of adequate contraceptive efficacy of Yvidually was obtained from the interim analysis of an ongoing trial with Yvidually where the calculated PI was 0 with an upper limit of the 95% confidence interval of 1.0, which is considered conclusive in terms of precision of the Pearl Index.

Bleeding pattern of the dosing regimen

Compared to the conventional YAZ 24+4 dosing regimen (6 days/year), the number of days of intracyclic bleeding was comparable in the YAZ Flex MB regimen (5 days/year), but more frequent in the YAZ Stop & Go (14.8 days/year).

On the other hand, the number of withdrawal bleedings decreased from 12 times/year (YAZ 24+4) to 4.6 and 4.5 times/year (YAZ Stop & Go and YAZ Flex MB).

The mean duration of withdrawal bleeding was longer in the extended cycle regimens and the mean duration of the intracyclic bleeding episodes was higher when compared to YAZ 24+4 (7-8 days vs 5 days).

Further, the total number of bleeding days per year decreased from 66 (YAZ 24+4) to 41-47 days (YAZ Stop & Go and YAZ Flex MB).

An overview is presented in the table below.

Table 4 Numbers of withdrawal episodes and intracyclic bleeding days per year

	Number of withdrawal bleeding episodes per year	Mean duration of the withdrawal bleeding episode	Derived number of bleeding days of withdrawal bleeding episodes	Derived number of intracyclic bleeding days per year	Total number of days of bleeding per year (withdrawal and intracyclic)
YAZ Flex MB*	4.5	8	36.0	5.0	41
YAZ Fixed extended*	2.8	10	28.0	33.0	61
YAZ Stop & Go	4.6	7	32.2	14.8	47
YAZ 24+4*	12.0	5	60.0	6.0	66

* Numbers taken from EU/CA study (A40196)

It is known and described in the SmPCs of all COCs that postponing a withdrawal bleed will introduce higher risk of intracyclic bleeding in most women. The longer the postponement the higher this risk, which is clearly shown in the fixed extended arm in which no break – no withdrawal bleed was allowed (33 days of intracyclic bleeding/year).

However, the noted slight increase in days of intracyclic bleeding or other bleeding problems were not shown to result in a high number of discontinuations: 8/888 (0.8%) in the EU/CAN study and 12/1406 (0.9%) in the US study. Therefore the data available do not indicate that the noted bleeding patterns had a negative impact on tolerability of the women choosing a flexible dose regimen in order to postpone withdrawal bleeding.

In the additional European study 14701, the bleeding pattern of the regimen applied for including use of the tablet dispenser was investigated. However only raw data on bleeding patterns were submitted and no analyses in this regard are available.

In summary, the data have demonstrated that compared to YAZ 24+4, the number of withdrawal episodes decreases as well as the total number of bleeding days over a period of 1 year, which is the aim of this product. Postponing a withdrawal bleed will introduce higher risk of intracyclic bleeding in most women, as is already known from current COCs, but the data available do not indicate that the noted bleeding patterns of Yvidually had a negative impact on tolerability of the women.

Tablet dispenser

The dispenser which has been designed to be an integral part of Yvidually in order to deliver tablets in line with the proposed dose regimen, has not been used in the pivotal studies. Only usability testing required by the Medical Device Directive 93/42 has been performed, which is considered to be acceptable since a medical device that is intended to administer a medicinal product is governed by the Directive 93/42, without prejudice to the provisions of Directive 2001/83 with regard to the medicinal product.

The applicant has also provided interim results of the additional study 14701 with Yvidually and the tablet dispenser. In this study, two versions of the dispenser – with or without acoustic alarm – are

compared. Only very limited data from the interim analysis are currently available. Most women rate the dispenser as easy to use and have no difficulties in understanding the Quick reference card, User manual, and Symbol Guide. There are no signals that the compliance is less than that reported in the initial clinical studies, in which a paper + pencil was used to adhere to the dose regimen. The CHMP requested the applicant to submit the final results of the study 14701 when available, to show that the use of the dispenser positively influences the compliance of Yvidually.

In summary, usability of the dispenser is considered acceptable and confirmed by the interim data of the additional dispenser study.

2.3. Risk management plan

A RMP has been submitted and agreed upon during the preceding Decentralised Procedure on Yvidually.

2.4. Recommendation

Yvidually has been developed for women who want to postpone the monthly withdrawal bleeding, occurring with the marketed combined oral contraceptive YAZ 24+4 by extending the intake cycle up to 120 days.

It is concluded that contraceptive efficacy of Yvidually has been sufficiently demonstrated for the proposed dosing regimen of Yvidually that allows the woman to decide herself to take a 4-day tablet-free interval or not during the flexible phase. Evidence is primarily based on the pearl indices obtained in an EU/Canada study that allowed a 4-day tablet-free interval in case of 3 consecutive days of bleeding and/or spotting (Flex MB regimen). The reason for the break (bleeding occurrence or woman's own choice) will not influence the contraceptive efficacy, as long as the general rules of intake will be adhered to, that is regular uninterrupted daily tablet intake for at least 24 days and tablet-free intervals of a maximum of 4 days between intake cycles. No significant differences in number of cycles and mean cycle length were observed when a 4-day tablet-free interval was recommended irrespective of bleeding and/or spotting (Stop & Go regimen). Moreover, with considerably less tablet-free intervals and longer periods of active treatment in both variants, efficacy will be at least as good as established for the currently authorised YAZ 24+4. Based on the above, the CHMP agreed that the results of the YAZ Flex MB regimen could be extrapolated to the proposed dosing regimen of Yvidually.

Further supportive evidence of adequate contraceptive efficacy of Yvidually was obtained from the interim analysis of an ongoing trial with Yvidually where the calculated PI was 0 with an upper limit of the 95% confidence interval of 1.0, which is considered conclusive in terms of precision of the Pearl Index.

The data have adequately demonstrated that compared to YAZ 24+4 (conventional regimen), the number of withdrawal episodes decreases as well as the total number of bleeding days over a period of 1 year, which is the aim of this product. As expected with an extended dosage regimen, different bleeding patterns have been observed, but the data available do not indicate that the noted bleeding patterns of Yvidually had a negative impact on tolerability of the women.

Interim analysis of the additional study 14701 with Yvidually and the tablet dispenser indicates that women rate the dispenser as easy to use, and that there are no signals that it adversely affects compliance. The applicant should submit to the National Competent Authorities the final results of the study 14701 by 28 February 2013.

2.5. Conclusions and benefit risk assessment

Having considered the overall submitted data provided by the applicant,

- The Committee reviewed all available data submitted by the applicant to address the potential serious risk to public health, in particular concerning the contraceptive efficacy of the proposed extended dosing regimen.
- The Committee considered that the overall efficacy has been sufficiently proven by the data presented, in particular the EU/Canada study. The Committee considered that the benefit/risk of Yvidually and associated names in the applied indication and extended dosing regimen is considered to be favourable.

the CHMP was of the opinion that the benefit/risk of Yvidually and associated names in the applied indications is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation subject to recommended conditions with regard to the safe and effective use of the medicinal product as set out in Annex IV of the CHMP opinion. The summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion subject to the conditions of the marketing authorisation as set out in Annex IV of the CHMP opinion.

Appendix 1

Divergent positions

Article 29(4) referral of Council Directive 2001/83/EC, as amended

Procedure No: EMEA/H/A-29/1330

Yvidually (INN: ethinylestradiol and drospirenone)

Divergent statement

Based on the presented clinical evidence in their totality, we are of the following opinion:

As proposed by the Applicant, the extrapolation of the results obtained in the Yaz Flex MB regimen arm to Yvidually cannot be accepted. Indeed, although the US Study was not powered to obtain adequate precision for the Yaz Stop and Go regimen Pearl Index (PI), the higher PI (3.52; 95% CI 1.29 - 7.67) compared to the Yaz Flex MB and the Yaz 24 + 4 regimens in the same study (1.65 and 1.20 respectively) is of concern. The argument put forward by the Applicant, that the lower duration of exposure in the Yaz Stop and Go arm compared to the Yaz Flex MB arm (1 year vs 2 years) may explain the difference regarding Pearl Indexes, cannot be accepted. Indeed, the duration of exposure in the Yaz extended and Yaz arms in the US study is also 1 year but the Pearl Indexes are much lower (0.00 for Yaz extended and 1.20 for Yaz). Although the mean cycles' length is similar between Yaz Stop and Go and Yaz Flex MB regimens in the US Study, the above discussed elements suggest that the PIs may be different and underline the need to have a reliable PI calculated for the Yaz Stop and Go regimen (Yvidually regimen).

In addition, Yvidually will be available with a tablet dispenser which was not used in the pivotal studies. Although the tablet dispenser supports the proposed posology, the way the women will use the dispenser in real life influences the compliance and thus the Pearl Index of Yvidually. Yvidually comprises tablets and a tablet dispenser and should have been evaluated in pivotal clinical trials as an entity.

A study (study 14701) with Yvidually and the tablet dispenser involving 500 women in five european countries is still on-going (results awaited in October 2012), however no conclusion on the contraceptive efficacy can be drawn on the submitted interim results. Indeed, only data after 6 months of treatment are available, when the CHMP guideline on clinical investigation of steroid contraceptives mentioned that at least 400 women should have completed one year of treatment.

In conclusion, we are of the opinion that the contraceptive efficacy of the Yvidually still remains to be substantiated.

CHMP members expressing a divergent opinion:

Pierre Demolis (FR)	19 July 2012	Signature: .....
Jens Heisterberg (DK)	19 July 2012	Signature: .....
Agnes Gyurasics (HU)	19 July 2012	Signature: .....
Natalja Karpova (LV)	19 July 2012	Signature: .....
David Lyons (IE)	19 July 2012	Signature: .....
Daniela Melchiorri (IT)	19 July 2012	Signature: .....
Jan Mueller-Berghaus (DE)	19 July 2012	Signature: .....
Harald Enzmann (DE)	19 July 2012	Signature: .....