# Public Assessment Report

# Scientific discussion

# Talia 0.02 mg/3 mg film-coated tablets (ethinylestradiol/drospirenone)

## NL/H/2917/001/DC

## Date: 7 October 2014

**This module reflects the scientific discussion for the approval of Talia 0.02 mg/3 mg film-coated tablets. The procedure was finalised on 10 April 2014. For information on changes after this date please refer to the module 'Update'.**

**This report includes a summary, on pages 12-14.**

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Talia 0.02 mg/3 mg film-coated tablets from Qualitec Europa, S.L.

The product is indicated for oral contraception. The decision to prescribe this contraceptive pill should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Talia 0.02 mg/3 mg compares with other CHCs (see sections 4.3 and 4.4 of the approved SmPC).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the European reference product Yaz 24+4 0.02 mg/3 mg film-coated tablets (NL license RVG 33842), from Bayer B.V., authorised in the Netherlands since 29 June 2007. This is a fixed dose combination of 3 mg drospirenone and 0.02 mg ethinylestradiol.

For the applied product, an optional extended dose regimen is proposed which is comparable with the extended dose regimen approved for Yvidually (NL/H/2014/001/DC), also known as Yaz Flex and Flexyess. Yvidually, approved in October 2012, is a specific form of Yasminelle and Yaz, and was developed by the innovator in combination with a tablet dispenser system to guide the woman during a flexible dosing phase to delay menstruation with a maximum of 120 days. As the dose regimen of this product deviates from the reference product Yaz/Yasminelle, the application is submitted according to Article 10(3). For substantiation of the application, the MAH refers to studies performed with Yvidually.

As for Yvidually, the intended dosing regimen for Talia is to have a minimum duration of 24 consecutive days of dosing, with three options for ongoing dosing after the first 24 days:
1. Extended use, to a maximum of 120 consecutive days.
2. A four-day pill-free break, to be initiated when the woman experiences bothersome unscheduled bleeding/spotting.
3. A four-day pill-free break, to be initiated electively whenever a woman chooses to schedule her withdrawal bleed.

Under all three options, each pill-free break would be followed by at least 24 consecutive days of dosing. Unlike Yvidually, Talia is not supplied with a tablet dispenser.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Talia 0.02 mg/3 mg is a pink, round film-coated tablet of 5.7mm diameter.

The film-coated tablets are packed in clear to slightly opaque Aluminium/PVC-PVdC blisters containing 24 film-coated tablets. A carton box contains five blisters, *i.e.* a total of 120 tablets.
Each package of Talia comes with thirty-five (5x7) adhesive stickers which have the days of the week printed on them.

The excipients are:
*Tablet core* - lactose monohydrate, pregelatinised starch (maize), sodium croscarmellose, povidone K-30 (E1201), polysorbate 80, magnesium stearate (E572)
*Coating* - polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc (E553b), yellow iron oxide (E172), red & black iron oxide (E172)

## II.2 Drug Substance

***Ethinylestradiol***

The active substance ethinylestradiol is an established active substance, described in the European Pharmacopoeia (Ph.Eur.). It is a white or slightly yellowish-white crystalline powder, which is practically insoluble in water and freely soluble in alcohol. It dissolves in dilute alkaline solutions. Ethinylestradiol exhibits only one not solvated polymorphic form.

The CEP procedure is used for the active substance ethinylestradiol. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP. An additional test for one residual solvent is included. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data have been provided.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

***Drospirenone***
The active substance drospirenone is an established active substance, described in the Ph.Eur. It is a white or almost white powder. Water solubility is 10.9 mg/l. Drospirenone does not show polymorphic forms. The CEP procedure is used for this active substance.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is based on the Ph.Eur. monograph and the CEP with additional tests for one residual solvent. The specifications are acceptable in view of the route of synthesis and the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. No special storage conditions are required. The assessment was part of granting the CEP and has been granted by the EDQM.

## II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The product development objective was to develop film-coated tablets that would be bioequivalent to the medicinal product Yasminelle®, having the same qualitative and quantitative composition in drug substances per tablet and the same pharmaceutical form.
A water based wet granulation process was tried and experimental batches were tested and dissolution profiles were compared to the dissolution profile of the reference product.
Dissolution profiles at three different pH values were determined for test and reference batches used in the bioequivalence studies.
Additionally, a comparison of three industrial validation batches against the bioequivalence pilot batch and both reference products was performed. It was shown that all profiles are comparable. Sufficient *in-vitro* data have been presented.
A compatibility study was performed to describe potential interactions between the individual excipients and the active drug substances.
The container closure system (PVC-PVdC/aluminium blisters) is usual for this type of dosage form.

Manufacturing process

The drug product is manufactured by wet granulation. The process consists of blending, granulation, drying, milling, tablet compression and coating. The in-process controls for the manufacturing process of the tablets are acceptable. The manufacturing process has been adequately validated according to relevant European Guidelines.

Control of excipients
All excipients are tested in accordance with their respective Ph.Eur. monograph, except for Opadry® II Pink, which is tested according to in-house procedures. The specifications are acceptable.

Quality control of drug product
The drug product specification includes tests for appearance, identification (release only), dissolution, assay, related substances, content uniformity (release only), residual solvents (release only) and microbial control. For appearance, dissolution, drospirenone assay, drospirenone related substances and microbial control, the shelf-life specifications are the same as the release specifications. For assay of ethinylestradiol, the shelf-life specification is wider than the release specification, which is supported by stability data.
The analytical methods have been adequately described and validated. The HPLC methods for assay and related substances are considered to be stability indicating.
Batch analytical data for two pilot batches and three industrial batches of the drug product have been provided, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the drug product have been provided on two pilot-scale and three commercial-scale batches. The batches were stored at 25°C/60% RH (36 months for the pilot-scale and 12 months for the commercial-scale batches), 30°C/65% RH (12 months for two commercial scale batches) and 40°C/75%RH (6 months for all batches). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-Al blisters.
A photostability study in compliance with the NfG on Photostability Testing has been performed, which shows that the product is not sensitive to light. In view of the provided stability data, the claimed shelf-life of 36 months and the proposed storage conditions “Store below 30ºC” were granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE declarations have been provided for lactose monohydrate and lactose anhydrous, as they are of animal origin.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Talia film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Talia is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Yaz 24+4, which is available on the European market. Reference is made tot the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

Drospirenone and ethinylestradiol are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this hybrid application, the MAH has submitted a bioequivalence study, which is discussed below under section IV.2 'Pharmacokinetics'.

## IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test products Talia 0.02 mg/3 mg (Qualitec Europa, S.L., Spain) is compared with the pharmacokinetic profile of the reference products Jasminelle 3.0 mg/0.02 mg film-coated tablets (Bayer Sante, France).

*The choice of the reference product*
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
*Design*
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy females of childbearing potential, aged 20-43 years old. Each subject received a single dose of three tablets (3 x 3 mg/0.02 mg) of one of the 2 drospirenone/ethinylestradiol formulations. The tablets were orally administered with 240 ml water after a fasting period of at least 10 hours. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120 hours after administration of the products.

The design is acceptable for this kind of application, the wash-out of 28 days is sufficient and the sampling period long enough. Furthermore, the sampling scheme is adequate to estimate pharmacokinetic parameters. The administration of 3 tablets was considered necessary to achieve measurable plasma ethinylestradiol levels and justified by dose-linearity of drospirenone (1–10 mg) and ethinylestradiol (20–60 µg). This is acceptable.

*Results*
Two subjects withdrew and did not show up for the second period of the study. Therefore a number of 32 subjects completed the study. However, one subject was excluded from the analysis since pre-dose concentrations of >5% of $C_{max}$ were observed in both periods for both compounds. Statistical analysis was performed with 31 subjects.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of drospirenone under fasted conditions.

| **Treatment N=31** | **$AUC_{0-t}$** µg.h/ml | **$AUC_{0-\infty}$** µg.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 1.3 ± 0.3 | 1.4 ± 0.4 | 85 ± 15 | 1.75 | 32.7 |
| **Reference** | 1.3 ± 0.3 | 1.4 ± 0.4 | 85 ± 17 | 1.75 | 31.9 |
| ***Ratio (90% CI)** | 1.00 (0.97-1.02) | 1.00 (0.98-1.02) | 1.01 (0.94-1.07) | -- | -- |
| **CV (%)** | 5.1 | 5.1 | 14.9 | -- | -- |

| | | | | | |
|---|---|---|---|---|---|
| **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity<br>**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration<br>**$t_{1/2}$** half-life | | | | | |

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of ethinylestradiol under fasted conditions.

| **Treatment N=31** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** pg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 1.4 ± 0.3 | 1.6 ± 0.3 | 142 ± 29 | 1.75 | 32.7 |
| **Reference** | 1.5 ± 0.3 | 1.7 ± 0.3 | 147 ± 29 | 1.75 | 31.9 |
| ***Ratio (90% CI)** | 0.95 (0.90-0.99) | 0.95 (0.90-0.99) | 0.96 (0.91-1.02) | -- | -- |
| **CV (%)** | 11.1 | 10.5 | 13.8 | -- | -- |
| **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity<br>**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration<br>**$t_{1/2}$** half-life | | | | | |

**ln-transformed values*

The 90% confidence intervals calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of drospirenone and ethinylestradiol under fasted conditions, it can be concluded that Talia 0.02 mg/3 mg and Jasminelle, 3.0 mg/0.02 mg, film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A significant treatment effect was observed for the $AUC_{(0-\infty)}$ of ethinylestradiol and a significant period effect for the $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of drospirenone. The observed treatment effect is considered due to the high power of the study and therefore clinically not relevant since bioequivalence has been shown. The period effect for drospirenone is neither judged to influence the conclusion of the study since only 1 case of a pre-dose level was detected and therefore no carry-over effect could be concluded.

Drospirenone/ethinylestradiol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substances. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

## IV.1 Flexible dosage regimen

The clinical overview report submitted by the MAH refers to 65 publications up to year 2012. A justification is given for authorization of the product to be marketed with an optional adaptable regimen of up to 120 days, based on clinical studies present in the registration file of Yvidually.

With regard to the justification of the dosage regimen, the MAH concluded the following:

- Talia film-coated tablets contain a formulation of DRSP-EE 3 mg-0.02 mg which has demonstrated to be bioequivalent to the formulation developed by Bayer and marketed as Yasminelle®, Yaz® or Yaz® Flex (Flexyess/Yvidually).
- The optional flexible extended regimen of up to 120 days proposed for Talia is intended to extend the menstrual cycle and enable management of intracyclic (breakthrough) bleeding. This flexible extended regimen has already been authorized for the formulation developed by Bayer based on clinical trials supporting its efficacy and tolerability.
- DRSP-EE 3 mg/0.02 mg administered in a flexible extended regimen with management of intracyclic (breakthrough) bleeding is well-tolerated and, when administered for up to 2 years, has a safety profile comparable to other combined oral contraceptives.
- It has been demonstrated that known risks and potential risks are the same when Yaz® is administered in a 24/4-day regimen or in a flexible extended regimen of up to 120 days, therefore, no additional safety study is considered to be necessary to support the authorization of Talia in the same flexible extended regimen.

Initially, the proposed optional extended dose regimen was not completely similar to Yvidually. In response to the objections raised, the MAH has brought the extended flexible dosing regimen in line with that of Yvidually, *i.e.* a regimen with:

- A mandatory phase (day 1-24) and
- A flexible phase (day 25-120) with three different dosing options.

Yvidually has been developed with an electronic tablet dispenser with a reminder function to guide the woman through the intake regimen.
The electronic dispenser provides the user with information regarding the day of the current treatment cycle, whether the user may or should take the 4-day tablet free interval.

The hybrid product applied for, Talia, is not supplied with a dispenser. In order to guide the woman in using the 3 different dose regimens, the MAH added in the original application three charts which were incorporated in section 3 of the package leaflet (PL): a card for the mandatory phase, a card for option 2, *i.e.* a flexible phase (days 25-120) in which the break is related to breakthrough bleeding, and a card for option 3, a flexible phase in which the woman decides to have a 4-day break when it suits her best.
The MAH submitted the results of a readability test on the PL. The charts were however not assessed in this test, and there is no clinical experience with the 3 charts. Further, it was unclear how these charts should be used in clinical practice, e.g. if these should be cut out of the PL. Moreover, with the 5 blisters in one pack the woman can schedule a 4-day pill free break 5 times, whereas only 3 charts were incorporated in the PL. The Board was of the opinion that adequate use of the 3 charts is questionable. Therefore the MAH decided to remove these charts from the SmPC and PL. Section 3, 'How to use Talia', includes proper instructions for the user on the mandatory and flexible phases, and the options for taking a 4-day tablet-free interval. Therefore no additional chart or dispenser is provided.

The number of adhesive stickers included in the package has also been discussed during the procedure. The user might need more choice of stickers to be flexible during the different phases and to finish remaining tablets. With a sufficient number of stickers, the user can choose a new week sticker in the flexible phase and stick the new week sticker on top of the previous week sticker. However, when the user decides to use the product with the conventional dosing scheme (mandatory phase only), she needs the same week sticker for every blister. Since the package includes 5 blisters, the number of week stickers should be 35 (5x7). This number of stickers is included in the final common product information.

## IV.2 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Talia 0.02 mg/3 mg film-coated tablets.

**Summary table of safety concerns as approved in RMP**

| | |
|---|---|
| Important identified risks | Venous thromboembolism<br>Arterial thromboembolism<br>Breast cancer |

| | |
|---|---|
| | Benign and malignant liver tumours<br>Disturbances of liver function<br>Pancreatitis<br>Increased blood pressure<br>Effect on hereditary angioedema |
| Important potential risks | Cervical cancer<br>Worsening of endogenous depression<br>Crohn's disease and ulcerative colitis<br>Insulin resistance<br>Hyperkalemia<br>Delayed diagnosis of pregnancy |
| Important missing information | - |

The safety concerns included in the RMPs are considered appropriate. The member states agreed that routine pharmacovigilance activities and routine risk minimisation activities are considered sufficient for this product. The MAH has committed to follow the MAH of the reference product once any actions based on the additional pharmacovigilance activities are required.

### IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Yaz and Yvidually 0.02 mg/3 mg film-coated tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product.
The flexible regimen is in accordance with the regimen approved for Yvidually, and its usability has been sufficiently demonstrated. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The PL of Talia 0.02 mg/3 mg film-coated tablets is generally harmonized with the PL of the reference product Yaz 24+4, except for sections which include information regarding the extended dose regimen. These sections are generally harmonized with the PL for Yvidually.
The MAH adapted the PL according to the outcome of the Commission Decision of the Article 31 referral (procedure EMEA/H/A-31/1356) regarding combined oral contraceptives.

A readability test on the PL has been carried out in order to fulfill the legal requirements of the applicable EU legislation. The chosen participants for the readability test represent the population who would use Talia, in normal conditions. The selected women were aged between 18 and 55 years, variable educational backgrounds and occupations, variable social status, and Spanish as the principal language. A population of variable education levels was selected. The questions were designed to cover the parts of the leaflet where a clear understanding by the patient is necessary.
The test was performed by face-to-face interviews. The developed questionnaire contained 15 questions specific to the content of the package leaflet and 1 open question regarding general comments from the participant regarding the PL.
A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PL, and 90% of all participants can show that they understand and can act upon it. The data showed that overall the result met the passing criteria in the first and second round. Based on quantitative and qualitative results, there were no revisions to the PL after the first and second round of testing. There were sufficient questions about the critical sections. The results of the test were satisfactory. The readability test has been sufficiently performed.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Talia 0.02 mg/3 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Yaz 24+4 0.02 mg/3 mg film-coated tablets. Yaz is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

In the Board meeting of 9 January 2014, the proposed guidance for using the 3 different dose regimens was discussed. The Board decided that the inclusion of charts in the package leaflet is unsatisfactory to warrant compliance. The benefit/risk profile was however considered positive, provided that the charts would be deleted, and a clear description of the 3 regimens would be included in the product information. The MAH adapted the product information as required.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Talia 0.02 mg/3 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 April 2014.

There were no post-approval commitments made during the procedure.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| | | | | | | |

# Summary Public Assessment Report

# non-generics

# Talia 0.02 mg/3 mg film-coated tablets

# (ethinylestradiol and drospirenone)

## NL/H/2917/001-002/DC

## Date: 7 October 2014

# Summary Public Assessment Report

# non-generics

Talia 0.02 mg/3 mg film-coated tablets

Active substances: ethinylestradiol and drospirenone

This is a summary of the public assessment report (PAR) for Talia film-coated tablets. It explains how these medicines were assessed and the authorisations recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Talia.

For practical information about using this medicine, users should read the package leaflet or contact their doctor or pharmacist.

**What is Talia and what are they used for?**
Talia 0.02 mg/3 mg film-coated tablets is a 'hybrid generic medicine'. This means that it is similar to a reference medicine containing the same active substance: Yaz 24+4 0.02 mg/3 mg, film-coated tablet.

Talia is a contraceptive pill that contains two different female hormones. It is used to prevent pregnancy. The difference between Yaz 24+4 and Talia is that a flexible dosing regimen can be applied with Talia (see below).

**How does this medicine work?**
The combination of the two hormones in these pills, oestrogen and progestogen hormones, suppresses ovulation and prevents the release of an egg-cell during the menstrual cycle. It also thickens the mucus in the cervix, making it difficult for semen to enter the uterus. In addition, it thins the lining of the uterus, making it less likely that a fertilised egg can attach to it.

**How is this medicine used?**
The pharmaceutical form of Talia is a film-coated tablet and the route of administration is oral. The medicine can only be obtained with a prescription. The package contains five blisters. Each blister contains 24 film-coated tablets. Tablet intake starts with a 'mandatory phase' of 24 days, followed by a 'flexible phase' from day 25 to 120:

<u>Mandatory phase (day 1-24)</u>
Start by taking a pill marked with the correct day of the week. When starting, the tablets must be taken continuously for a minimum of 24 days, after which the user can either:
- stop taking tablets for a 4-days tablet-free interval during which her period will start,
- or continue to take them for up to 120 days (see flexible phase) by which she can delay het period.

<u>Flexible phase (day 25-120)</u>
During the days 25-120, the tablets can be taken continuously up to a maximum of 120 days (when all five blisters included in the package will be finished). Within this period, the user may decide for herself if she wants to take a 4-day tablet-free interval. With the 4-day tablet-free period, the withdrawal bleed will start.
In the event of continued bleeding (three consecutive days) during the tablet-taking period in the flexible phase (days 25-120), it is advisable to take a 4-day table-free interval which will induce a regular withdrawal bleed. This 4-day tablet-free interval will reduce the total number of days with bleeding.

A tablet-free interval should never be longer than 4 days and it should only be started if tablet taking has been continued for 24 days. During the 4-day tablet-free interval bleeding usually occurs and may not have finished before the next tablet intake cycle is started. After each 4-day tablet-free interval, a new intake cycle of a minimum of 24 days should be started, to a maximum of 120 days. After the mandatory phase of 24 days of continuous tablet taking, the user may again choose when to have the tablet-free 4 day interval between days 25 and 120.

It is recommended to start a new blister, which contains 24 tablets, for the mandatory phase and after a 4-day tablet free interval in order to make it easier to correctly follow the proper product administration.

To help the user remember to take the contraceptive, every package of Talia comes with fourteen adhesive stickers which have the days of the week printed on them. The user should choose the week sticker that starts with the day she begins taking the tablets. For example, if she starts on a Wednesday, the week sticker that starts with “WED” should placed on top of the blister.

Please read section 3 of the PL for detailed information on how to use this medicine.

**How has this medicine been studied?**
Because Talia is a hybrid medicine, studies in patients have been limited to tests to determine that the tablets are bioequivalent to the reference medicine, Yaz. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects from this medicine?**
Because Talia is a hybrid medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as those for Yaz.

**Why is this medicine approved?**
It was concluded that, in accordance with EU requirements, Talia has been shown to have comparable quality and to be bioequivalent to Yaz. Therefore, the Medicines Evaluation Board of the Netherlands decided that, as for Yaz, the benefits are greater than its risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of this medicines?**
A risk management plan has been developed to ensure that these medicines are used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Talia, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

**Other information about these medicines**
In the Netherlands, the marketing authorisations for Talia 0.02 mg/3 mg film-coated tablets was granted on 21 May 2014.

The full PAR for these medicines can be found on the website http://mri.medagencies.org/Human.
For more information about treatment with Talia, read the package leaflet (http://mri.medagencies.org/download/NL_H_2917_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in October 2014.