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prometrium

progesterone

400mg soft vaginal capsules

Formulary Application Pack

Prometrium (400mg soft vaginal capsules)[1]

Prometrium is indicated for the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages[1]

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to Besins Healthcare (UK) Ltd. Drug safety on 0203 862 0920 or email drugsafety@besins-healthcare.com

All product complaints should be reported to complaints@besins-healthcare.com

Please contact Besins Healthcare (UK) Ltd Medical Information on:
Tel: 01748 828 789
Email: besins@eu.propharmagroup.com

This formulary pack is intended to support the adoption of Prometrium onto local formularies.

Information within this formulary pack includes data from the Summary of Product Characteristics and supporting efficacy and pharmacokinetic data. It should be used as a repository of information that can help complete local formulary applications. For additional information, please contact Besins Healthcare UK medical information at besins@eu.propharmagroup.com

Prescribing information can be found on page 13 at the end of this document.

MAT-PROMO-PTM-0056 | June 2025

Prometrium (progesterone) Formulary Application Pack contents page

1. Miscarriage, Women's Health and the use of licensed medicines

Recurrent miscarriage

A miscarriage is the early loss of a pregnancy at some point during the first 24 weeks of pregnancy. About 1 in 5 pregnancies miscarry and most miscarriages occur within the first 12 weeks, but since many miscarriages aren't recorded, the number may be higher.[2]

In the UK, recurrent miscarriage means having three or more miscarriages, even if there are healthy pregnancies in between and it affects about one in every hundred couples trying to conceive.[3] Testing after recurrent miscarriage can be offered to try and find the cause. These tests can include genetic testing, blood clotting problems, testing for an abnormally-shaped uterus or cervical weakness and hormonal problems.[3]

Until the marketing authorisation of Prometrium 400mg soft vaginal capsules, there have been no other licensed treatments for recurrent miscarriage. Prometrium 400mg soft vaginal capsules is indicated for the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages.[1]

In this and other therapeutic areas, Healthcare Professionals should always choose licensed medicines wherever possible.[4]

The impact of miscarriage

The grief and psychological impact of miscarriage is often not comprehended.[5]

Miscarriage can be isolating. Many women do not share the news of their pregnancy until they reach 12 weeks, and a woman may not tell their family, friends, colleagues or even their partner about an early pregnancy loss. Many women and their partners suffer from this grief in silence, as psychological effects of miscarriage may have little or no outward physical manifestation, and so can go unrecognised by healthcare professionals, family and friends.[5]

According to the NHS, miscarriage can have a profound emotional impact on the woman, her partner, friends and family.[6] In a literature review of 9 studies, compared to women with no previous history of miscarriage (11%) , the risk of miscarriage increases by around 10% for each additional miscarriage, reaching 42% in women with three or more previous miscarriages.[7]

The Women's Health Strategy for England recognises that miscarriage is a common complication of pregnancy but it remains a taboo subject, and there is not enough focus placed on this and other women specific issues.[8]

Prometrium is licensed for the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages[1] and is currently the only licenced medicine available for this condition.[1]

Formulary inclusion of Prometrium can contribute to policy initiatives such as the Women's Health Strategy for England by boosting health outcomes.

NICE guidance 126, Royal College of Obstetricians and Gynecologists (RCOG) Green-top guidelines, and European Society of Human Reproduction and Embryology (ESHRE) guidance support the use of progesterone in women presenting with bleeding in the first trimester of pregnancy with a history of recurrent miscarriage.[9-11]

2. Medicine summary

2.1 Name of medicine[1]

Prometrium 400mg soft vaginal capsules

2.2 Licensed indication[1]

For the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages.

2.3 Strength and form of preparation[1]

One soft vaginal capsule contains 400 mg progesterone for vaginal administration only, 25mm by 9mm. Oblong soft yellowish capsule. Contains soyabean lecithin and a whitish oily suspension.

2.4 Dose and scheduling of administration[1]

The recommended dose is one vaginal capsule twice a day (morning and night) inserted deep into the vagina.

Treatment should always be individualised to the patient. The decision to treat women who have experienced recurrent miscarriages should follow further investigation and is at the discretion of the clinician.

Treatment should be initiated during the first trimester of pregnancy, at first sign of vaginal bleeding and should continue to the 16th week of gestation.

2.5 Proposed place in therapy[1]

1. Prometrium (progesterone) summary of product characteristics:[1]

- First trimester bleeding and history of recurrent miscarriage
- Perform a complete medical examination; investigate vaginal bleeding
- Ensure no contraindications before initiation of Prometrium (progesterone) 400mg vaginal capsules twice daily
- Continue Prometrium until 16th week gestation

2. The Royal College of Obstetricians and Gynaecologists (RCOG) recommends:[10]

- Progestogen supplementation should be considered in women with recurrent miscarriage who present with bleeding in early pregnancy (for example 400 mg micronised vaginal progesterone twice daily at the time of bleeding until 16 weeks of gestation).[10]

- **Evidence quality 1–B[10]**
    - 1: Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
    - B: A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+

3. National Institute for Health and Care Excellence (NICE) recommends.[9]

- In a 2021 amendment, NICE Guidance 126 suggests offering vaginal micronised progesterone 400mg twice daily to women with an intrauterine pregnancy confirmed by scan if they have vaginal bleeding and have previously had a miscarriage. In 2021 NICE recognised this as an off label use of progesterone.
- If a fetal heartbeat is confirmed, continue progesterone until 16 completed weeks of pregnancy. [2021]

4. European Society of Human Reproduction and Embryology (ESHRE) Recurrent Pregnancy Loss (RPL) Guideline[11]

a. Vaginal progesterone (twice daily 400mg progesterone) during early pregnancy (started <12 weeks) may have a beneficial effect in women with unexplained RPL (16 to 39-years old) with vaginal bleeding and it is therefore recommended to use:

i. Vaginal progesterone (twice-daily 400mg progesterone)
ii. Use from presentation to 16 completed weeks of gestation) to improve live birth rate in a subsequent pregnancy.

The strength of this evidence was regarded as 'conditional' and the quality of evidence rated 3 out of 4.

3. Summary of evidence

3.1 Mechanism of action[1]

Progesterone is a natural endogenous hormone of the corpus luteum and is the most important hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Prometrium is a body identical micronised progesterone, with induction of a full secretory endometrium and in particular has a gestagenic, anti-oestrogenic, slightly anti-androgenic and anti-aldosterone effects.

The pharmacodynamic effects for threatened and recurrent miscarriage are that progesterone modulates maternal immune responses to protect the foetus, improves the utero-placental circulation, maintains cervical integrity throughout pregnancy, promotes myometrial relaxation, inhibits prostaglandin production, and possesses anti-inflammatory properties.

3.2 Pharmacokinetics[1]

Administered vaginally, Prometrium provides a local effect on the vagina and uterus. The efficacy of vaginal progesterone is related to the overall amount of progesterone accumulating in the endometrium and not to the amount that is systemically absorbed.

Absorption

Micronised progesterone is rapidly absorbed following vaginal administration. Unlike oral progesterone, vaginal progesterone does not undergo first pass metabolism in the gastrointestinal tract and liver. As a result of the "uterine first pass effect", relatively high concentrations occur in uterine and nearby tissues with low systemic exposure to progesterone and its metabolites.

The plasma exposure following administration of different vaginal dosages (e.g. 200 mg to 600 mg) is non-linear and increases less than proportional to dose. In a reported clinical study, vaginal administration of 600 mg daily dose of progesterone resulted in stable plasma concentrations throughout administration times with the highest average plasma concentration equal to around 11.6 ng/ml.

Distribution

Vaginally accumulated progesterone undergoes the first metabolic cycle in the uterus, causing higher hormone levels in the uterus and nearby tissues. The small amount of progesterone that is absorbed is transported via the lymph and blood vessels and approximately 96 - 99% is bound to serum proteins, mainly into serum albumin (50 - 54%) and transcortin (43 - 48%).

Biotransformation

After vaginal administration observable plasma levels of pregnenolone and 5α - dihydroprogesterone are very low due to the lack of first-pass metabolism.

Elimination

95% of systemically absorbed progesterone is eliminated from the urine as glucorone conjugated metabolites.

3.3 Interactions[1]

Prometrium may interact with the following medications and investigations:

- Bromocriptine: may interfere with the effects of bromocriptine
- Ciclosporin: may raise the plasma concentration of ciclosporin
- Laboratory tests of hepatic and/or endocrine functions: may affect results
- Rifamycin medicines (e.g. rifampicin) and antibacterial agents: may accelerate metabolism of Prometrium
- Ketoconazole: may increase bioavailability

3.4 Contraindications[1]

- Hypersensitivity to the active substance or to any of the excipients
  - Sunflower oil, refined
  - Soyabean lecithin
  - Gelatin
  - Glycerol [E422]
  - Titanium dioxide [E171]
- Jaundice
- Severe hepatic dysfunction
- Undiagnosed vaginal bleeding
- Mammary or genital tract carcinoma
- Thrombophlebitis
- Thromboembolic disorders
- Cerebral haemorrhage
- Porphyria
- Allergy to nuts or soya

3.5 Special warnings[1]

- A complete medical examination must be performed before starting the treatment and regularly during the treatment.
- Prometrium should only be used for threatened miscarriage during the first trimester; up to the 16th week of pregnancy and must only be administered by the vaginal route.
- Prometrium is not suitable as a contraceptive.
- Treatment should be discontinued upon diagnosis of a missed abortion.

3.6 Precautions for use[1]

- **Vaginal bleeding:** any vaginal bleeding should always be investigated.
- **Soya or peanut allergy:** contains soybean lecithin and may cause hypersensitivity reactions. As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Prometrium.

3.7 Special populations[1]

- Paediatric population: no relevant use.
- Elderly patients: no relevant indication for use.

3.8 Adverse reactions[1]

- Local intolerance (burning, itching or oily discharge) has been observed, but the incidence is extremely rare.
- When used as recommended, transient fatigue or dizziness may occur within 1 – 3 hours of taking the medicine.
- Pruritus, vaginal discharge, vaginal haemorrhage and burning sensation have all been reported but the frequency is not known (cannot be estimated from the available data)

4. Efficacy and Safety

4.1 Efficacy and Safety

(PRISM trial) PRISM [Progesterone in Spontaneous Miscarriage]: a randomised trial of progesterone in women with bleeding in early pregnancy[12]

Coomarasamy A, et al. *Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy.* N Engl J Med. 2019 May

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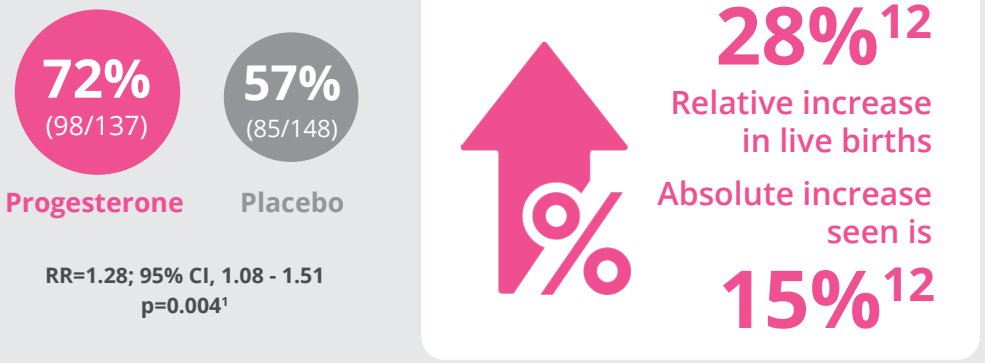
Study design	A multi-centre, randomised, double-blind, placebo-controlled trial comparing vaginal progesterone to placebo.
Objectives	To investigate whether treatment with 400mg vaginal progesterone suppositories or matching placebo, twice daily from the time they presented with bleeding through 16 weeks of gestation, would result in a higher incidence of live births among women with bleeding in early pregnancy than placebo.

Population	Women aged 16-39 years with pregnancy <12 weeks and vaginal bleeding from 48 UK hospitals.
Efficacy Results	**The primary endpoint of incidence of live births after at least 34 weeks of gestation was not met.** Of a total of 4153 eligible women from 48 hospitals in UK; 2079 received progesterone, 2074 received placebo. The incidence of live births after at least 34 weeks of gestation was 75% (1513 of 2025 women) in the progesterone group and 72% (1459 of 2013 women) in the placebo group (relative rate, 1.03; 95% confidence interval [CI], 1.00 to 1.07; P = 0.08). The sensitivity analysis, in which missing primary outcome data were imputed, resulted in a similar finding (relative rate, 1.03; 95% CI, 1.00 to 1.07; P = 0.08). The incidence of adverse events did not differ significantly between the groups.
Post hoc subgroup analysis – recurrent miscarriage	In a subgroup analysis of patients that had suffered recurrent miscarriage progesterone 400mg twice daily, such as Prometrium, was found to increase the chance of live births compared to placebo. **Live birth rate (%) in women with ≥3 previous miscarriages[12]** 
Efficacy Conclusions	Among women with bleeding in early pregnancy, progesterone therapy administered during the first trimester did not result in a significantly higher incidence of live births than placebo. The benefit reached statistical significance in the prespecified subgroup of women with three or more previous miscarriages and current pregnancy bleeding.
Safety Results	There was no significant between-group difference in the percentage of participants who had either a maternal or neonatal serious adverse event (5% [105 of 2025 participants] in the progesterone group and 5% [98 of 2013 participants] in the placebo group), including specifically the percentage of babies who had neonatal congenital abnormalities (3.4% in each group), nor was there any significant between-group difference in the number of maternal or neonatal serious adverse events.
Safety Conclusions	The incidence of adverse events did not differ significantly between the groups and no evidence of an increase in congenital abnormalities or short-term harm. Local intolerance (burning, itching or oily discharge) has been observed. When used as recommended, transient fatigue or dizziness may occur within 1 to 3 hours of taking the medicine. Vaginal discharge and haemorrhage have been reported, the frequency of which is unknown. Please refer to the SmPC for further information.[1]

4.2 Efficacy and Safety

(PROMISE Trial) PROMISE [Progesterone in recurrent Miscarriage]: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages[13]

Coomarasamy A, et al PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation. Health Technol Assess. 2016 May

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Study design	An international multi-centre, double blind, placebo-controlled, randomised trial.
Trial objective	To test whether or not progesterone therapy in the first trimester could reduce the risk of miscarriage in women with a history of unexplained recurrent miscarriage.
Population	Women aged 18-39 years with unexplained RM (recurrent miscarriage) in the first trimester of a naturally conceived pregnancy randomised to twice daily vaginal suppositories containing either 400 mg of micronised progesterone (n=398) or matched placebo (n=428) from a time soon after a positive urinary pregnancy test (up until 6 weeks) through 12 weeks of gestation.
Efficacy Results	The live birth rate in the progesterone group was 65.8% (262/398) and in the placebo group it was 63.3% (271/428), giving a relative risk of 1.04 (95% confidence interval 0.94 to 1.15; p = 0.45). There was no evidence of a significant difference between the groups for any of the secondary outcomes.
Safety Results	This trial incurred only one SUSAR (suspected unexpected serious adverse reaction), namely development of a rash by a single participant for whom study medication was discontinued and antihistamines were prescribed. The rash subsided within 48 hours. There was no difference between the treatment and the placebo group for the outcomes of "any congenital anomaly" (8/266 progesterone arm, 11/276 placebo arm, P=0.54) and "genital congenital anomaly" (1/266 progesterone arm, 1/276 placebo arm, P=0.98).

Category	Progesterone (N=404), n (%)	Placebo (N=432), n (%)
Allergy	2 (0.5)	0 (0.0)
Dermatological	1 (0.2)	3 (0.7)
Gastrointestinal	20 (5.0)	14 (3.2)
Haematological	0 (0.0)	1 (0.2)
Neurological	7 (1.7)	4 (0.9)
Urological	3 (0.7)	4 (0.9)
Miscellaneous	8 (2.0)	4 (0.9)

Safety Conclusions	This study was the largest-ever randomised placebo-controlled clinical trial to report on the treatment effects of first-trimester progesterone therapy for pregnant women with a history of unexplained RM. In addition to the efficacy results described above, vaginal progesterone capsules 400 mg twice daily is a well-tolerated drug to use in early pregnancy with no evidence of an increase in congenital abnormalities or short-term harm.

4.3 A critical evaluation of the PROMISE [Progesterone in recurrent Miscarriage] and PRISM [Progesterone In Spontaneous Miscarriage] trials by the study authors[14] Coomarasamy, Arri, et al. *"Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence."* American journal of obstetrics and gynecology 223.2 (2020)	
Study design	A critical evaluation of the PROMISE and PRISM studies. The PROMISE and PRISM study authors reviewed the effects of first trimester use of vaginal micronised progesterone previously evaluated in 2 large, high-quality, multi-centre placebo controlled trials. One trial targeted women with unexplained recurrent miscarriages (the PROMISE [Progesterone in recurrent Miscarriage] trial) and the other targeting women with early pregnancy bleeding (the PRISM [Progesterone In Spontaneous Miscarriage] trial).
Objectives	To assess what the PROMISE and PRISM studies add to existing knowledge, to review of the evidence for key prespecified subgroup effects using robust guidelines and provide recommendations for clinical practice.
Population	The PROMISE trial studied 836 women from 45 hospitals in the United Kingdom and the Netherlands. The PRISM trial studied 4153 women from 48 hospitals in the United Kingdom.
Results	The PROMISE trial found a 3% greater live birth rate with progesterone but with substantial statistical uncertainty. The PRISM trial found a 3% greater live birth rate with progesterone, but with a P value of 0.08, **meaning that the endpoint was not met.** A key finding, first observed in the PROMISE trial, and then replicated in the PRISM trial, was that treatment with vaginal micronised progesterone 400 mg twice daily was associated with increasing live birth rates according to the number of previous miscarriages. Prespecified PRISM trial subgroup analysis in women with the dual risk factors of previous miscarriage(s) and current pregnancy bleeding fulfilled all 11 conditions for credible subgroup analysis. For the subgroup of women with a history of 1 or more miscarriage(s) and current pregnancy bleeding, the live birth rate was 75% (689/914) with progesterone vs 70% (619/886) with placebo (rate difference 5%; risk ratio, 1.09, 95% confidence interval, 1.03-1.15; P=.003). The benefit was greater for the subgroup of women with 3 or more previous miscarriages and current pregnancy bleeding; live birth rate was 72% (98/137) with progesterone vs 57% (85/148) with placebo (rate difference 15%; risk ratio, 1.28, 95% confidence interval, 1.08-1.51; P=.004).
Summary	Women with a history of miscarriage who present with bleeding in early pregnancy may benefit from the use of vaginal micronised progesterone 400 mg twice daily.

5. Anticipated impact

List price drug acquisition

Formulation	Drug	Preparation	Manufacturer	Dosing	NHS list price	PIP Code
Vaginal capsule	Prometrium 400mg	400 mg progesterone capsules	Besins Healthcare (UK) Ltd.	400mg twice daily	£20.00 for 15 capsules	435-0674

Besins Healthcare (UK) Ltd. have submitted a confidential discounted price to the Medicines Procurement and Supply Chain (MPSC) which has been accepted. Please speak to your local pharmacist for details of the discounted price.

Anticipated rates of recurrent miscarriage

The exact prevalence of recurring pregnancy loss (RPL) is very difficult to estimate, as both the numbers in the numerator (experienced RPL) and the denominator (women at risk of RPL, all women at fertile age, or all women who try to get pregnant), are difficult to obtain.[11]

Recurrent pregnancy losses affect about 1% of couples who attempt to conceive.[10,15] In 2021, the number of conceptions for women of all ages in England and Wales was 824,983.[16]

Please consider your local population when calculating the possible impact of Prometrium 400mg to your healthcare system.

6. Contact us

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Medical Information:

01748 828 789

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7. References

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8. Prescribing information

PROMETRIUM (progesterone) 400mg SOFT VAGINAL CAPSULES

For full product information, including side effects, precautions and contraindications, please consult the Summary of Product Characteristics (SmPC).

Presentation: Prometrium 400mg soft vaginal capsules, each capsule contains 400mg of progesterone. **Indication:** Prometrium 400mg soft vaginal capsules is indicated for the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and who have a history of recurrent miscarriages. **Posology and method of administration:** Each capsule must be inserted deep into the vagina. Recommended dose is 400mg twice a day. Treatment should be initiated during the first trimester of pregnancy, at first sign of vaginal bleeding and should continue to the 16th week of gestation. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, jaundice, severe hepatic dysfunction, undiagnosed vaginal bleeding, mammary or genital tract carcinoma, thrombophlebitis, thromboembolic disorders, cerebral haemorrhage, porphyria, allergy to nuts or soya. **Warnings and Precautions:** Prometrium 400mg soft vaginal capsules should only be used up to the 16th week of pregnancy and must only be administered vaginally. Prometrium 400mg soft vaginal capsules is not suitable as a contraceptive. Treatment should be discontinued upon diagnosis of a missed abortion. Any vaginal bleeding should always be investigated. Contains soybean lecithin and may cause hypersensitivity reactions: urticarial and anaphylactic shock in hypersensitive patients. As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Prometrium 400mg soft vaginal capsules. A complete medical examination must be performed before starting the treatment and regularly during the treatment. **Interactions:** May interfere with the effects of bromocriptine and may raise the plasma concentration of ciclosporin. May affect the laboratory tests of hepatic and/or endocrine functions. Metabolism is accelerated by rifamycin medicines and antibacterial agents. **Fertility, pregnancy and lactation:** No association has been found between the maternal use of natural progesterone in early pregnancy and foetal malformation. Prometrium 400mg soft vaginal capsules is not indicated during breastfeeding. Detectable amounts of progesterone enter the breast milk. As this medicinal product is indicated to prevent miscarriage in women, there is no known deleterious effect on fertility. **Effects on ability to drive and use machines:** Can have a moderate influence on the ability to drive and use machines. **Undesirable effects:** local intolerance (burning, itching or oily discharge) has been observed, but the incidence is extremely rare. When used as recommended, transient fatigue or dizziness may occur within 1 to 3 hours of taking the medicine. Pruritis, vaginal discharge, vaginal haemorrhage and burning sensation have been reported, the frequency of which is unknown. **Overdose:** symptoms of overdosage may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and if necessary, symptomatic and supportive measures should be provided.

NHS List Price: Prometrium 400mg soft vaginal capsules £20.00 for 15 capsules. **Legal Category:** POM **Marketing Authorisation Number:** PL 28397/0014. **Authorisation Holder:** Besins Healthcare, 80 Rue Washington, 1050 Ixelles, Belgium **Date of Preparation:** January 2025 MAT-PROMO-PTM-0003

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Email: pharmacovigilance@besins-healthcare.com