Amber with Guidance (Amber-G) = To be recommended or initiated by a specialist with follow up prescribing and monitoring by primary care clinicians.*
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Barnsley Hospital NHS Foundation Trust | South West Yorkshire Partnership NHS Foundation Trust | Barnsley Clinical Commissioning Group

Clomifene for the treatment of women with infertility due to ovulatory dysfunction.

The details of side-effects, cautions, contraindications and interactions are not a complete list and the current BNF **(https://bnf.nice.org.uk/drug/clomifene-citrate.html#indicationsAndDoses)** and the SPC **(Clomid 50mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)** remain authoritative.

Background Information	• The specialist initiating Clomifene should advise the GP on the initiation of the drug via discharge papers or through a clinic letter.
BNF therapeutic class	• 8.1a Anti-Oestrogens. Ovulation Stimulants
Indication	• Clomifene is licensed for females with infertility due to ovulatory dysfunction. Other causes of infertility must be excluded or adequately treated before giving Clomifene. • It is an anti-oestrogen which induces gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; chorionic gonadotrophin is sometimes used as an adjunct.
Dosage and administration	• The recommended dose for the first course of Clomifene is 50mg daily for 5 days starting on day 2 of the cycle (this leads to an increased chance of recruitment of follicles and thus ovulation). Commencing Clomifene on day 2, 3, 4 or day 5 is acceptable, though beyond that window, the chance to recruit a follicle is lost. This is repeated for 3 cycles until a 3 month review where progesterone levels will be measured and assessed. • For patients who are amenorrhoeic, As long as there is a negative pregnancy test, Clomifene can be started on any day for a total of 5 days with or without progesterone withdrawal. A pregnancy test is mandatory before commencing Clomifene if progesterone withdrawal is not undertaken. • If progestin-induced bleeding is planned, or if spontaneous uterine bleeding occurs before therapy, the regimen of 50mg daily for 5 days should be started on the 2nd day of the cycle. When ovulation occurs at this dosage, there is no advantage to increasing the dose in subsequent cycles of treatment, however it does lead to an increased risk of multiple pregnancy and rarely ovarian hyper-stimulation. • The guidance of starting Clomifene on day 2-5 is for patients who either have spontaneous bleeding or who have a withdrawal bleed. • If the patient has no period after any cycle, they will require a pregnancy test. If there is a period, the patient should take Clomifene for a second month and then a third month, then reviewed at 3 months after progesterone levels are taken (day 21 after cycle 3). • If ovulation appears not to have occurred after the first 3 cycles of therapy, the dose of Clomifene will be increased to100mg daily for 5 days.This course may be started as early as 30 days after the previous one. Increase of dosage or duration of therapy beyond 100mg/day for 5 days should not be undertaken. • The majority of patients who are going to respond will respond to the first course of therapy, and 6 courses should constitute an adequate therapeutic trial (the effect of Clomifene is cumulative therefore six cycles at minimum dose gives the best chance of conception) • If ovulatory menses have not yet occurred, the diagnosis should be re-evaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation. • Clomifene 50mg Tablets are available

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Cautions and Contraindications	• **Cautions:** - Clomifene is ineffective in patients with primary pituitary or primary ovarian failure. - Ectopic pregnancy - Incidence of multiple births increased - Ovarian Hyperstimulation syndrome - Polycystic ovary syndrome - Uterine fibroids • **Contraindications:** - Pregnancy - Patients with liver disease or a history of liver dysfunction - Patients with hormone dependant tumours or in patients with abnormal uterine bleeding of undetermined origin. - Patients with ovarian cysts (except polycystic ovary) as enlargement of the cyst may occur. Patients should be evaluated for presence of ovarian cyst prior to each course of treatment.
Pregnancy and breast feeding	Pregnancy should be excluded before treatment as there are possible effects on the development of the foetus and Clomifene may inhibit lactation.
Adverse Drug Reactions	• Adverse effects appeared to be dose-related, occurring more frequently at the higher dose and with the longer courses of treatment used in investigational studies. At recommended dosage, adverse effects are not prominent and infrequently interfere with treatment. • During the investigational studies, the more commonly reported adverse effects included ovarian enlargement (13.6%), vasomotor flushes (10.4%), abdominal-pelvic discomfort (distention/bloating) (5.5%), nausea and vomiting (2.2%), breast discomfort (2.1%), visual symptoms (1.5%), headache (1.3%) and intermenstrual spotting or menorrhagia (1.3%). • alopecia; angioedema; anxiety; breast tenderness; cataract; cerebral thrombosis; depression; disorientation; dizziness; fatigue; headache; hot flush; hypertriglyceridaemia; insomnia; jaundice cholestatic; menstrual cycle irregularities; mood altered; nausea; neoplasms; nervous system disorders; ovarian and fallopian tube disorders; palpitations; pancreatitis; paraesthesia; psychosis; seizure; skin reactions; speech disorder; stroke; syncope; tachycardia; uterine disorders; vertigo; vision disorders; visual impairment (discontinue and initiate ophthalmological examination); vomiting • Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme: www.mhra.gov.uk/yellowcard
Interactions	• None stated
Additional information	• Patient advice: Patients planning to conceive should be warned that there is risk of multiple pregnancy (rarely more than twins).

Contact names and details

Contact Details	Telephone number	Email
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- Include out of hours contact details where available
- Insert web details of department or trust information page
- Where relevant/available insert web details and/or phone numbers of specialist support groups

References

- British National Formulary (BNF). NICE. Accessed 2021. Available at: https://bnf.nice.org.uk/drug/clomifene-citrate.html
- Summary of Product Characteristics. Clomid 50mg tablets. August 2020. Available at: https://www.medicines.org.uk/emc/product/961/smpc%201 Accessed October 2021

https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

Development Process

This guidance has been produced by Lauren Clarke (Senior Pharmacist – Interface) following an AMBER-G classification status of Clomifene by the Barnsley Area Prescribing Committee. This guideline was ratified by the Area Prescribing Committee on 9th February 2022.