Study Protocol

A double blind placebo controlled trial of a combination of methotrexate and gefitinib versus methotrexate alone as a treatment for ectopic pregnancy

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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Amendments

Number and Ethics Date	Amendment Type	Summary of Changes Made
01_3rd March 2016	Following ethical review	Changes as per feedback from ethics.
02_8th March 2016	Non-substantial	Questionnaire v3_typos corrected Protocol, timescales clarified, unblinding, randomisation process detailed, minor clarifications to inclusion/exclusion as per clinician's feedback
03_10th October 2016	Non-substantial	Correction of typo on page 19, Japanese ethnicity added for consistency.
01_1st September 2016	Substantial protocol v 5	Clarification of terms following co-investigators, TSC and DMC meetings
02_6th October 2016	Substantial	Addition of sites
03_1st December 2016	Substantial	Addition of sites
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PROTOCOL APPROVAL

GEM3: A double blind placebo controlled trial of a combination of methotrexate and gefitinib versus methotrexate alone as a treatment for ectopic pregnancy

EudraCT number 2015-005013-76

Signatures

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Name		17th May 2021
Chief Investigator	**Signature**	**Date**
Name		17 – May - 2021
Trial Statistician	**Signature**	**Date**
Name	Fiach O'Mahony	17 May 2021
Lead Co-Sponsor Representative	**Signature**	**Date**

NB Image of signatures put on protocol – wet ink signatures held in TMF

I confirm that I have read this protocol and will perform all trial duties as specified within this.

_____	_____	_____
Principal Investigator	Signature	Date

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AR	Adverse Reaction
AZ	Astra Zeneca
CI	Chief Investigator
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
EGFR	Epidermal Growth Factor Receptor
EP	Ectopic Pregnancy
GCP	Good Clinical Practice
hCG	Human chorionic gonadotrophin
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IU/L	International Units/Litre
IVF	In vitro Fertilisation
MTX	Methotrexate
PI	Principal Investigator
PUL	Pregnancy of unknown location
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TK	Tyrosine Kinase
TMF	Trial Master File
UAR	Unexpected Adverse Reaction

SUMMARY

DESIGN:	A multi-centre double-blind placebo-controlled randomised trial of a combination of methotrexate and gefitinib versus methotrexate and placebo alone as a treatment for ectopic pregnancy.
PICO:	Population: Women 18-50 with a diagnosis of EP being managed medically with MTX Intervention: Combination MTX with gefitinib Comparator: MTX treatment and matched placebo Outcome: surgical treatment of index EP
SETTING:	Approximately 70 NHS hospitals within the UK
TARGET POPULATION:	• 328 women diagnosed with a haemodynamically stable tubal EP diagnosed on ultrasound with serum hCG concentrations ≥1000 IU/L and ≤5000 IU/L. 328 randomised to receive single-dose intramuscular MTX (50mg/m2) injection routine care) with either daily doses oral gefitinib (250mg) or matched placebo for 7 days. **INCLUSION CRITERIA** • Clinical decision made for treatment of tubal EP with MTX • Able to understand all information (written and oral) presented (using an interpreter if necessary) and provide signed consent • 18-50 years at time of randomisation • **Diagnosis of either;** 1. definite tubal EP (extrauterine gestational sac with yolk sac and/or embryo, without cardiac activity on USS) **or** 2. clinical decision of probable tubal EP (extrauterine sac-like structure or inhomogeneous adnexal mass on USS with a background of sub optimal serum hCG concentrations (on at least 2 different days)) • Pre-treatment serum hCG level of 1000–5000 IU/L (within 1 calendar day of treatment) • Clinically stable • Haemoglobin between 100 and 165 g/L within 3 calendar days of treatment • Able to comply with treatment and willing to participate in follow up **EXCLUSION CRITERIA** • Pregnancy of unknown location (PUL) • Evidence of intrauterine pregnancy • Breastfeeding • Hypersensitivity to gefitinib • EP mass on ultrasound greater than 3.5cm (mean dimensions) • Evidence of significant intra-abdominal bleed on USS defined by echogenic free fluid above the uterine fundus or surrounding ovary within 1 calendar day of treatment • Significant abdominal pain, guarding/rigidity • Clinically significant abnormal liver/renal/haematological indices noted within 3 calendar days of treatment • Galactose intolerance • Significant dermatological disease eg severe psoriasis/eczema • Significant pulmonary disease eg severe/uncontrolled asthma • Significant gastrointestinal illness eg Crohn's disease/ulcerative colitis • Participating in any other clinical trial of an investigational medicinal product • Previous participation in GEM3 • Japanese ethnicity
HEALTH TECHNOLOGIES ASSESSED:	Blinded allocation to either methotrexate and gefitinib or methotrexate and placebo
OUTCOME MEASURES:	PRIMARY CLINICAL OUTCOME: surgical intervention for treatment of index EP. SECONDARY CLINICAL OUTCOMES: 1) additional MTX 2) time to hCG resolution (days) from randomisation to hCG level of ≤15 IU/L 3) number of treatment-associated hospital visits until resolution or scheduled/emergency surgery 4) safety/tolerability 5) acceptability of treatment (assessed after 3 months post resolution by Likert score) 6) return to menses (assessed after 3 months post resolution of EP)
ANALYSIS:	Analysis will be by intention to treat. Every attempt will be made to gather data on all women randomised, irrespective of compliance with the treatment protocol. Point estimates, 95% confidence intervals and p-values from two-sided tests will be calculated for all main outcome measures. A Statistical Analysis Plan will be drawn up prior to any analysis and reviewed by the independent Data Monitoring Committee. We will use a log-binomial regression model adjusting for the minimisation variables to calculate the relative risk and 95% confidence for the primary outcome; a chi-squared test will be used to determine statistical significance of the group parameter in the model. Other dichotomous secondary outcomes (e.g. need for additional treatment) will be analysed in the same fashion as the primary outcome. Time from randomisation to successful resolution will be will be analysed using a Cox Proportional Hazard model. Standard methods will be used to analyse other outcomes. Tests for statistical heterogeneity will be performed prior to any examination of effect estimate within subgroups. Sensitivity analyses will be performed on the primary outcome to investigate the impact of missing data.
SAMPLE SIZE:	: Based on data from our Phase I and II studies (GEM1 and 2), and data from an Edinburgh/Imperial 2012 cohort undergoing usual care, we have designed the study to be able to detect a reduction from 30% to 15% in surgical intervention rate with 90% power and alpha error 5%. This will require 164 participants per group, 328 in total (allowing for a 2% loss to follow-up rate).

LAY SUMMARY

Tubal ectopic pregnancy (EP) occurs when an embryo implants in a Fallopian tube rather than the uterus. If the pregnancy continues to grow there may be stretching and ultimately rupture of the tube causing life-threatening, internal bleeding. Fortunately, in countries where ultrasound scans and pregnancy hormone (hCG) blood testing are widely available, most EP are now diagnosed before they rupture. Management of an unruptured EP depends on symptoms, pregnancy size, presence of internal bleeding, and hCG measurement. When a patient has a high risk of rupture as evident from severe symptoms, a large EP, internal bleeding or a high hCG level, then surgery is the best treatment. In the remaining women, a methotrexate (MTX) injection is a suitable treatment. However, in 30% of women, MTX treatment is unsuccessful (with surgery still required). In 15% of women, it is partially effective (2nd dose of MTX required). For many women, treatment is prolonged (many hospital visits) adding to emotional distress. A more effective treatment is necessary to reduce the need for emergency surgery, the requirement of repeat treatment and the prolonged time to complete treatment. Gefitinib is a drug taken orally that is licensed to treat a type of lung cancer. We have performed three small studies using MTX and gefitinib. In the first study (laboratory based), we found that EP tissue regresses in response to gefitinib and that it improves the effect of MTX. In the second and third studies (called GEM1 and GEM2), we found that giving MTX and gefitinib together to women with EP may reduce the need for surgery and reduced hospital visits. Using the drugs together did not cause any important side effects. These findings now require further study in a large trial and we need to reach a better understanding of how gefitinib works. We therefore will conduct a clinical study to compare using MTX and gefitinib together with using MTX and placebo (dummy drug), to study how gefitinib works in the body. All of the women who agree to participate in the trial will receive MTX (normal treatment dose) and also be randomly allocated to take either a gefitinib, or a placebo tablet, once a day for 7 days. We will assess whether the two drugs together are better than MTX with placebo at treating the EP without the need for surgery. We will also compare how long the hCG level takes to decrease, number of hospital visits and need for further MTX, as well as safety and patient satisfaction between the study groups. To monitor treatment response, we will collect blood samples as per local routine clinical, this is usually three times in the first eleven days after treatment then weekly to measure hCG levels until they drop to non-pregnant levels. The study will recruit 328 women from up to 70 UK hospitals. We may ask women in whom the treatment has failed and who require ‘rescue’ surgery for permission to collect their pregnancy tissues from local pathology departments. This tissue is taken and kept at sites as part of routine care. This will allow us to examine the microscopic effect of MTX and gefitinib on ectopic pregnancy tissues. We believe that our trial will show the drugs together will be of greater benefit to women with EP in terms of fewer operations, hospital visits and blood tests.

INTRODUCTION

1.1 BACKGROUND

Ectopic pregnancies

Ectopic pregnancies are pregnancies that implant in maternal tissues other than the specialised endometrium of the uterus, most often in one of the Fallopian tubes. They are still one of the leading causes of maternal death in the first trimester. This is because placental trophoblastic cells are invasive by nature, and outside of the relatively controlled environment of the uterus, are able to erode into maternal blood vessels and cause sometimes fatal internal bleeding.

Ectopic pregnancies are common, accounting for approximately 2% of all pregnancies (Lancet. 2005 366(9485):583-91). Rates are thought to be rising due to increasing IVF use, increasing maternal age and pelvic infections. Thus, ectopic pregnancy is a significant gynaecological disease. While prompt diagnosis and management make deaths in the developed world rare, maternal mortality from this condition is still significant. In The United Kingdom, 6 deaths occurred as a result of ectopic pregnancies between 2006-2008 (CEMACE 2011). In the developing world, women diagnosed with an ectopic pregnancy have up to 100 times increased mortality compared to the developed world (Obstet Gynecol 2004;103:692-697). Lack of timely access to lifesaving surgery and limited medical-only options are likely contributors to this significant mortality rate.

We currently treat ectopic pregnancies in one of three ways:

1. Occasionally, a woman is haemodynamically stable and serum levels of beta human beta chorionic gonadotrophin (βhCG) indicate that the pregnancy is already resolving , allowing conservative management in tracking the βhCG through to resolution (≤15 IU/L).

2. Medical management is an option in some centres with the appropriate resources and in patients who will attend regularly for follow-up. It consists of a single (or sometimes multiple) dose(s) of intramuscular methotrexate (MTX) 50mg/m^2, and similarly requires the woman to be haemodynamically stable.

3. The majority of ectopic pregnancies are treated surgically, where the pregnancy (and most often the Fallopian tube it is found in) is removed. Any signs of haemodynamic instability in a woman with an ectopic pregnancy mandate surgical management.

Medical Management

Current management

Methotrexate is a chemotherapeutic agent, a folic acid antagonist. It inhibits DNA synthesis and cell replication by competitively inhibiting the conversion of folic acid to folinic acid, with subsequent cytotoxic, immunosuppressive and anti-inflammatory actions (Cancer Chemotherapy and Biotherapy 1996; 109-148).

Successful medical management of ectopic pregnancy means the women will avoid surgery and its potential risks and retain their Fallopian tube. There are,

however, some significant limitations to medical treatment with MTX. It is a fairly non-specific agent, which targets all dividing cells and therefore unsurprisingly, has a substantial number of side effects. Furthermore, its efficacy has been shown to decrease with increasing ectopic pregnancy size. Thus, centres that offer MTX management of ectopic pregnancy generally offer this treatment option to women when the serum βhCG is less than 3000 IU/L, and pelvic ultrasound demonstrates a gestational sac of no more than 4cm in size, no fetal cardiac motion detected and only a moderate amount of pelvic free fluid. About 25% of women who present with an ectopic pregnancy fulfil such criteria and surgical management remains the primary treatment for ectopic pregnancies.

Potential new medical therapeutic option: gefitinib

The last fifteen years has seen the emergence of a new class of molecular therapies specifically targeting tyrosine kinase (TK) cell surface receptors, known as tyrosine kinase inhibitors (Nature Reviews Cancer **4**, 361-370). Developed mainly for cancer therapy, blockade of these receptors leads to decreases in cell survival, proliferation and angiogenesis. The specificity of their mechanism of action makes them much better tolerated and freer of significant toxicities compared to conventional chemotherapeutic agents. Tyrosine kinase domains are common to a number of transmembrane receptors, which has led to the development of increasingly specific drugs. In particular, the epidermal growth factor receptor (EGFR) has a TK domain, and the drug gefitinib has been developed to target it. It works by blocking autophosphorylation of the EGFR and therefore, its downstream cell signalling actions. The EGFR pathway is an attractive drug target since EGF is a potent cell survival molecule. Upon EGFR activation, a cascade of downstream molecules relay signals via well-known pathways (MAPK kinase, PIP3-Akt, Ras/MEP/ErK) to up-regulate expression of genes conferring proliferative, angiogenesis and cell survival (anti-apoptosis) properties.

Data from post marketing surveillance representing over 92,000 patients exists, and has shown that EGFR inhibitors are well tolerated and largely free of serious side effects (FDA report: Clin Cancer Res 2004;10:1212-8). Of note, the data on tolerability is based on patients taking gefitinib daily on an ongoing, indefinite basis, after primary treatment of a cancer. Diarrhoea and skin storage are the most common side effects (20-30%). The skin rash, described as acneiform, can be severe, but is generally self-limited. Interstitial lung disease (ILD) is a very rare but serious side effect of gefitinib. It is a thickening of the lung parenchyma that can be fatal in a third of cases. Of the 31,045 patients in the USA who took gefitinib (reported to the FDA), 84 developed ILD (1.3%). [See later for further discussion related to ILD].

1.2 RATIONALE FOR STUDY

Although gefitinib was designed for treatment of non-small cell lung cancer, we know from publicly available, independent microarray datasets, that placental tissue expresses EGFR >3000 fold higher than the average expression of all

human tissues. This is, by far, the highest expression of EGFR of all tissue types. Furthermore, there is direct evidence suggesting placental tissue is indeed heavily reliant on EGFR signalling for survival and ongoing viability (Hum Rep 2008;23:1733-41; Placenta 2005;26:548-55; Biol Reprod 2007;77:53-60). EGF signalling promotes cytotrophoblast motility, blocks trophoblast apoptosis and rescues placental cells from apoptosis when exposed to hypoxia or alcohol exposure. Therefore, EGFR blockade should negatively impact on trophoblast survival.

We hypothesised that adding oral gefitinib to MTX could be supra-additive in regressing placental tissue. If so, it could be a potent way to medically cure stable ectopic pregnancies of any size. We have previously reported an extensive body of preclinical laboratory studies to examine this hypothesis (Obstet Gynecol 2013; 745-751).

In-vitro, combination treatment results in a >70% decrease in placental cell viability. The xCELLigence system (measures electrical impedance across cells, taking measurements every 15 minutes) suggests placental cell death starts within 24 hours of combined treatment. Apoptosis (programmed cell death) was also enhanced with combination treatment. Pathway analysis suggested that the two drugs were converging to inhibit phosphorylation of the epidermal growth factor receptor on the placental cell surface and phosphorylation of the downstream signalling molecule AKT.

In-vivo, treatment with either agent resulted in xenograft tumour volume shrinkage in a dose-dependent manner. Combining these agents resulted in a supra-additive effect in terms of xenograft tumour shrinkage, tumour weight reduction and lowering serum hCG in mouse blood.

We thus concluded from these preclinical studies that placental tissue is exquisitely sensitive to combination MTX and EGFR inhibition (gefitinib), where these agents can induce potent cell death. Importantly, there is a supra-additive effect when the agents are combined. This is a consistent finding from previous combination of EGFR inhibitors with other cytotoxic agents in cancer patients.

We then undertook the first step in transferring this concept from the bench-top to the bedside, with a toxicity study in twelve women. Importantly for use in humans, we noted:

1. Safety profiles of these drugs are known. MTX is already used clinically for small ectopic pregnancies, so its use presents no ethical issues. Gefitinib (an EGFR inhibitor) - arguably the safer of the two drugs - is well tolerated, and is currently taken daily for life after primary treatment for non-small cell lung cancer. In this efficacy study, we propose adding seven daily doses of gefitinib to the single injection of MTX at the same dose already used clinically.
2. An excellent biomarker with which to gauge response exists. One of the key determinants of drug translation is the existence of a robust clinical biomarker to judge efficacy. For ectopic pregnancies, we can track treatment response with quantitative serum hCG, a very sensitive marker of viable trophoblast tissue. Thus, a sensitive measure of treatment efficacy exists to track progress, and we are not left to rely on late signs of possible rupture. We can offer prompt surgery,

or a second MTX injection, if hCG levels do not decline appropriately with treatment.

3. When used to treat cancer, gefitinib has limited efficacy because the lung cancer will often develop mutations which then makes it resistant to its actions. EGFR inhibitors are less effective if there are k-Ras mutations (which can activate downstream pathways independent of EGFR signalling), or in the presence of a mutation at the ATP-binding pocket (T790M mutation)).

In contrast, in our patients there will be no possibility of escape mechanisms and development of resistance since ectopic pregnancies are non-malignant tissue. Thus, unlike trials for cancer where success of the EGFR inhibitors is defined as progression free survival (in months), 'resolution' of ectopic pregnancy will be our primary outcome of interest.

Our toxicity study showed the combination of seven days of 250mg gefitinib tablets with the standard 50mg/m^2 intramuscular injection of MTX to be safe and well tolerated in the treatment of ectopic pregnancies, with no major side effects or toxicities experienced by participants (Obstet Gynecol 2013; 745-751). Although efficacy was not a primary outcome of this study, we noted a significant trend to faster resolution of ectopic pregnancies, as evidenced by rapidly declining hCG levels compared to historic controls.

We have recently completed a Phase II (GEM2) single arm open label multicentre clinical trial to evaluate the efficacy and side effects of a combination of a single dose of MTX and seven daily doses of gefitinib to treat 28 women with tubal EP (Protocol published in BMJ 2013). The primary outcome was the successful resolution of an EP to non-pregnant hCG levels. Women with tubal EP with hCG levels of 1000 IU/L to 10,000IU/L were studied, as recent data had emerged suggesting EP with serum hCG levels less than 1000 IU/L may be suitable for successful conservative management. The combination treatment successfully resolved 24/28 cases of EP (86%; 95%CI: 73% to 99%) and hence we accepted our study hypothesis of at least 70% efficacy. The four women requiring surgery had significantly higher pre-treatment serum hCGs (p=0.012) compared with the successful participants. Of note, the women who were eligible for the study, but not recruited and received MTX alone, had a 66% resolution of EP (21/32) without the need for surgery (RR 1.31 CI 0.97, 1.75; p=0.07). The combination treatment commonly caused transient rash and diarrhoea, but no serious adverse events.

We are ready to capitalise on the data from these two studies and perform a definitive adequately-powered clinical trial to determine the true efficacy and mechanism of action of a combination of MTX and gefitinib for the treatment of EP.

Potential Risks to Participants

Interstitial lung disease (ILD) is the most significant known adverse reaction to gefitinib, and something we have given serious consideration to in our study design. Causing ILD in a previously well young woman would obviously be untenable. It is worthwhile considering the following points however:

- ILD can occur with primary treatment of lung cancer (5-10% incidence with radiation or chemotherapy) and can occur with lung cancer even in the absence of treatment. The risk of ILD for cetuximab treatment (monoclonal antibody EGFR inhibitor) for colon cancer is extremely rare, with some parties contending no association. This supports the contention that the presence of lung cancer is an important contributory factor in the risk of developing ILD.

- The median time to developing ILD was 42 days (Clin Cancer Res 2004;10:1212-8). We propose stopping the medication after seven days to minimise risk.

- In existing data on gefitinib, there was an association between ILD and male sex, smoking and age >55 years (Clin Cancer Res 2004;10:1212-8). Our trial population by definition excludes men and people older than 55 years. We do not wish to exclude smokers. Smoking is itself a risk factor for ectopic pregnancy, and given the risks of developing ILD with the short length of treatment we propose is likely to be negligible, we propose including smokers in our trial. This is so we can offer this treatment to smokers in the future.

- There is a higher incidence in the Japanese population (1%), but not other SE Asian countries (0.3%) (Clin Cancer Res 2004;10:1212-8). In this study we will exclude women of Japanese ethnicity.

We plan to administer seven 250mg gefitinib tablets, one daily for seven days, in addition to MTX. This is an extremely short duration of treatment compared with gefitinib's current marketing indications and existing data usage. Our toxicity (dose-escalation) study for this indication and in the same target group, found the treatment to be safe and well tolerated, with no major side effects or toxicities experienced by participants (n=6) (Obstet Gynecol 2013; 745-751). We therefore believe that the risk to our participants of causing de novo ILD is negligible.

Potential Benefits

The management of an unstable patient with an ectopic pregnancy will always remain surgical, however, for the remaining 90-95%, we seek to broaden the eligibility criteria for medical management with the addition of gefitinib to the current regimen of single-dose MTX. The availability of a medical therapy that could resolve stable ectopic pregnancies of any size could significantly impact on contemporary gynaecological care, rendering the management of ectopic pregnancy a mainly medical condition. There may be important benefits:

Safer treatment for women: While the availability of skilled gynaecologists makes surgery generally safe, important risks remain. They include risks associated with a general anaesthetic, bleeding, infection and damage to vital internal organs. An alternative that avoids surgery would avoid the risks of these iatrogenic surgical complications.

Cost savings: Compared to the costs of surgery (staff costs, maintaining laparoscopic equipment, hospitalisation), a medical alternative that can treat most ectopic pregnancies would result in significant savings. A recent systematic meta-analysis suggested that systemic MTX protocols to treat small ectopic pregnancies (serum hCG <1500 IU/L) was cheaper than surgery by 52%, decreasing the cost per patient from 1585 to 756 Euros as a direct result of reduced theatre usage and hospital stay. However, use of current MTX protocols

for larger ectopic pregnancies (serum hCG >1500 IU/L) was not cost effective compared to surgery, due to a higher rate of surgical re-intervention as a result of treatment failure (Hum Reprod Update 2008;14:309-19).

Benefits for developing countries to reduce maternal mortality: In some parts of the developing world, the risk of dying from an ectopic pregnancy may be as high as 1 in 30 (Acta Obstet Gynecol Scand 2003;82:305-12). Reasons are likely to be both late diagnosis, and a lack of resources to provide costly surgical care. Being potentially cheaper and less complicated to administer, a medical treatment could be accessed by more women compared to surgery, possibly saving lives in the developing world.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

The current non-surgical management of women with a tubal ectopic pregnancy comprises the systemic administration of MTX. We aim to test the hypothesis that a combination of intramuscular MTX and oral gefitinib, an EGFR antagonist, is a more effective treatment than MTX alone. By conducting a high quality, multicentre double-blind randomised controlled trial comparing combination MTX and gefitinib with MTX and matched placebo, we will address the following objectives:

2.1.1 Primary Objective

1. To assess the effectiveness of a combination of MTX and gefitinib against MTX alone in terms of the need for surgical intervention for ectopic pregnancy

2.1.2 Secondary Objectives

1. To assess the effects of a combination MTX and gefitinib, compared with MTX treatment alone, on:
    a) The need for further treatment with MTX
    b) The number of days to resolution of the pregnancy (hCG ≤15 IU/L)
    c) The number of hospital visits associated with treatment until resolution or scheduled/emergency surgery

2. To assess the safety, tolerability and acceptability of combination MTX and gefitinib compared with methotrexate treatment alone.

ENDPOINTS

2.1.3 Primary Endpoint

Surgical intervention for treatment of the index EP (salpingectomy/salpingostomy by laparoscopy/laparotomy).

2.1.4 Secondary Endpoints

Clinical Endpoints

1. Additional MTX
2. Time to hCG resolution (days) from randomisation until hCG levels ≤15IU/L
3. Number of hospital visits associated with treatment until resolution or scheduled/emergency surgery
4. Safety/tolerability (adverse events)
5. Acceptability of treatment (assessed 3 months after resolution of EP by Likert score)
6. Return to menses (assessed 3 months after resolution of EP)

3 STUDY DESIGN

GEM3 is a multicentre, double blind randomised placebo controlled trial. Participants will be recruited from early pregnancy units, gynaecology outpatient departments, wards etc of participating centres, fitting around their current service provision. Recruitment will occur over a minimum period of 24 months. The treatment duration for each participant will be seven days. Standard clinical care will then be followed with serum hCG levels collected as per local protocols until hCG levels fall to non-pregnant levels (≤15IU/L) with a follow up at 3 months post resolution to determine return of menses and acceptability of treatment questions. This will be performed via a telephone call from local research teams. A blood sample (FBC, U&Es, LFTs) to monitor for adverse effects will be collected once, on or between, follow up days 14 and 21. Day of MTX treatment is defined as either day 0 or day 1 depending on local policies.

Please see appendix 3 for flowchart of study design.

4 STUDY POPULATION

We will be studying women diagnosed with a haemodynamically stable tubal EP diagnosed on ultrasound with serum hCG concentrations ≥1000 IU/L and ≤5000 IU/L. These women will only be recruited if they have been deemed suitable for MTX treatment by their attending clinical team as per local protocols.

4.1 NUMBER OF PARTICIPANTS

Based on data from phase I and II trials we aim to recruit a total of 328 participants. This number of participants will be able to detect a reduction from 30% to 15% in the rate of surgical intervention after medical treatment with 90% power (type I error 5%). Participants will be recruited over a period of at least 24

months from approximately 70 sites in the UK (number dependent on rate of recruitment).

4.2 INCLUSION CRITERIA

- Clinical decision made for treatment of tubal EP with MTX
- Able to understand all information (written and oral) presented (using an interpreter if necessary) and provide signed consent
- 18-50 years at time of randomisation
- **Diagnosis of either;**

1. definite tubal EP (extrauterine gestational sac with yolk sac and/or embryo, without cardiac activity on USS)
   OR

2. clinical decision of probable tubal EP (extrauterine sac-like structure or inhomogeneous adnexal mass on USS with a background of sub optimal serum hCG concentrations (on at least 2 different days))

- Pre-treatment serum hCG level of 1000–5000 IU/L (within 1 calendar day of treatment)
- Clinically stable
- Haemoglobin between 100 and 165 g/L within 3 calendar days of treatment
- Able to comply with treatment and willing to participate in follow up

4.3 EXCLUSION CRITERIA

- Pregnancy of unknown location (PUL)
- Evidence of intrauterine pregnancy
- Breastfeeding
- Hypersensitivity to gefitinib
- EP mass on ultrasound greater than 3.5cm (mean dimensions)
- Evidence of significant intra-abdominal bleed on ultrasound defined by echogenic free fluid above the uterine fundus or surrounding ovary within 1 calendar day of treatment
- Significant abdominal pain, guarding/rigidity
- Clinically significant abnormal liver/renal/haematological indices noted within 3 calendar days of treatment
- Galactose intolerance
- Significant pre-existing dermatological disease eg severe psoriasis/eczema
- Significant pulmonary disease eg severe uncontrolled asthma
- Significant gastrointestinal medical illness eg Crohn’s disease, ulcerative colitis
- Participating in any other clinical trial of a medicinal product
- Previous participation in GEM3
- Japanese ethnicity

4.4 CO-ENROLMENT

Participants will not be permitted to participate in any other IMP clinical trials. Participants will be permitted to take part in non-IMP research (e.g. questionnaire/tissue only studies). Participants will not be eligible if participated previously in GEM3. As per ACCORD Co-enrolment Policy (POL008 Co-enrolment Policy) no formal documentation or authorisation from the Sponsor is required.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Women with a diagnosis of tubal EP suitable for medical management with MTX who wish to be considered for the study will be referred by clinical staff to the clinical research team.

5.2 CONSENTING PARTICIPANTS

Eligible participants will be approached by a member of their clinical care team and informed of the study and provided with the participant information sheets. All eligible women will have the opportunity to discuss and ask questions about the study. Consent will only be taken once the patient has had adequate time to read the participant information sheet and had her questions answered. Consent may be taken by a member of the clinical care team who have had specific trial training and GCP training or targeted trial specific GCP training.

5.3 SCREENING FOR ELIGIBILITY

Local protocols will be followed for diagnosis of EP which will include; ultrasound scan, serum hCG levels, clinical history, examination (if clinically indicated) and routine serum biochemistry and haematology. These parameters will be used to determine whether the participants fulfil eligibility criteria if they express an interest in the study. Eligibility will be documented by a delegated clinician within the patient notes.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

No further information will be collected on women who are ineligible. Anonymised information will be collected on a screening log to capture all eligible participants whether recruited or not. Individuals who are not recruited to the trial will continue with standard clinical care.

RANDOMISATION

RANDOMISATION

https://www.trials.bham.ac.uk/GEM3

Telephone 0131 242 9492 (office hours)
Online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and occasional network problems.

After consent has been obtained, all eligibility criteria have been met randomisation can take place via web-based service provided by BCTU. Each centre and each randomiser will be provided with a unique username and password.

If for any reason the online randomisation is unavailable the randomiser can call the trial team on 0131 242 9492. This line is available Monday to Friday 09:30 to 16:30. Eligibility from the CRF must be answered before randomisation can take place. A temporary number will be given whilst the database is offline. The relevant pharmacy will then be contacted and a random treatment will be selected by the pharmacist. This will be documented in the accountability log. Details of this allocation will then be reconciled with the database and stratification adjusted as necessary.

Following randomisation, an email will be sent to the randomiser, local principal investigator, local research nurse, regional nurse, trial managerand pharmacist from the GEM3 trial's mailbox. This will confirm PIN, date of treatment and treatment bottle allocation.

Participants will be randomised individually into the GEM3 trial in an equal ratio of methotrexate/gefitinib or methotrexate/placebo. A minimisation procedure using a computer-based algorithm will be used to avoid chance imbalances in the following variables:

- Baseline hCG levels (<1500 IU/L, ≥1500 to <2500 IU/L, ≥2500 IU/L
- BMI (<25, ≥25)
- Ectopic size (<2cm, ≥2cm)
- Centre

To avoid any possibility of the treatment allocation becoming too predictable, a random factor will be included within the algorithm whereby allocation to the minimised treatment group will occur with probability less than one. Full details of the procedure will be stored in a secure confidential document at BCTU.

5.4.1 Treatment Allocation

Each trial participant will receive intramuscular MTX (50mg/m^2) as per local trust protocol plus either seven days of once daily 250mg oral tablet of gefitinib or matched placebo (1st dose to be taken after but on the same day of administration of MTX treatment).

As numbers of participants at some of the sites may be as low as 1 or 2 per year it is not practical or cost effective to have large numbers of drugs on the pharmacy shelves. The trial management team will electronically manage the drug supply via a bespoke database.

5.4.2 Emergency Unblinding Procedures

All participants will be given an emergency card to carry while participating in the study. This will contain contact numbers and drug information. Participation in the study will be documented in clinical notes and alerts placed on electronic or paper notes as per local protocols.
The mechanism for code breaking will be:

- An online code break facility will be part of the BCTU randomisation database with limited access to who can break the blind.

- Sponsor will have access to the randomisation database in case of potential SUSARs.

In the event of unblinding, whether accidental or deliberate e.g. due to a serious adverse event, the investigator must document the action taken and promptly notify the sponsor.

5.4.3 Withdrawal of Study Participants

Participation in the study is voluntary. A patient has the right to discontinue the drug or completely withdraw from the study at any time for any reason. The Investigator has the right to discontinue a patient taking the drug at any time if it is deemed to be in the patient's best interest.

If the patient is withdrawn due to a serious adverse event, the Principal Investigator (PI) will arrange for follow-up visits or telephone calls until the event has resolved or stabilised. However, the data will be used in the analysis unless consent is specifically refused by the participant.

It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Types of withdrawal as defined are:

- The participant would like to withdraw from trial treatment, but is willing to be followed up in accordance with the schedule of assessments. .
- The participant would like to withdraw from the trial and does not wish to be followed up but is happy for the data collected prior to withdrawal to be retained by the research team.
- On rare occasion of withdrawal of consent, the participant wishes to withdraw completely (i.e. from trial treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future trial analysis.

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data.
If a participant withdrawals for any of the above, no data will be destroyed. It will remain in the Trial Master File for any future audit or regulatory purposes.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

Gefitinib

6.1.1 Study Drug Identification

Gefitinib (EU/1/09/526) (trade name of Iressa®) - supplied as 250mg film coated tablet.

Note MTX (50mg/m^2) will be prescribed by the participant's attending clinician as per local clinical protocols and will be given intramuscularly by nursing staff. MTX is standard clinical care for the medical management of EP and is not a study drug.

6.1.2 Study Drug Manufacturer

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
Cheshire
SK10 2NA
Tel: +44(0)1582836000
Fax: +44(0)1582838000

6.1.3 Marketing Authorisation Holder

AstraZeneca AB
S-151 85
Sodertalje
Sweden
EU/1/09/526/001 and EU/1/09/526/002

6.1.4 Labelling and Packaging

AZ will provide the IMP then shipped to Sharp Services UK for clinical trial packaging and labelling.

6.1.5 Storage

Tablets stored in the hospital pharmacy will be stored at room temperature (<30°C) in original packaging in order to protect from moisture. The gefitinib have a shelf life of five years.

The trial drug packs containing gefitinib or placebo will be labelled by Sharp Clinical Services (UK) Ltd, Unit 28, Heads of the Valley Industrial Estate, Rhymney, Tredegar, NP22 5RL and held in pharmacy and will be dispensed only upon receipt of prescription. Where there is no access to a pharmacy, the drugs may be kept on the ward/with EPU with accountability logs kept in main pharmacy and only limited supply dispensed. Permission for this will be on strict criteria where controls for storage and temperature monitoring are met and agreed by the sponsor.

6.1.6 Summary of Product Characteristics or Investigators Brochure

The Summary of Product Characteristics (SmPC) gefitinib is given in Appendix 1 and for methotrexate Appendix 2.

6.2 PLACEBO

The placebo will be in tablet form and will also be manufactured by AstraZeneca (as above) labelled by Sharp. This will match the active drug. The placebo and active drug will appear identical.

6.3 DOSING REGIMEN

Participants will receive a seven-day supply of 250mg gefitinib or placebo tablets, to be taken once a day. They will be asked to take the gefitinib at approximately the same time each day.

If a dose is missed, participants will be advised that if it is less than 12 hours late they should take the missed tablet as soon as the participant remembers and take the next dose at the usual time. If they are more than 12 hours late they should be advised to skip the forgotten tablet and take the next one at the usual time. If the participant vomits after taking a tablet they should not take another that day but continue as normal the next day. Written instruction will be given to each participant.

6.4 DOSE CHANGES

No changes in dose permitted.

6.5 PARTICIPANT COMPLIANCE

Participants will be asked at each visit if they have taken the drug so that the researcher can record how much study drug has been taken. Participants will be

asked to return any unused drug to the research team for safe disposal in pharmacy. We anticipate that some participants may not take the complete course of trial medication for various reasons, e.g. withdrawal from treatment or surgical management. This will recorded on the CRF.

6.6 OVERDOSE

There is no specific treatment in the event of overdose of gefitinib. An increased frequency and severity of some adverse reactions may be observed, mainly diarrhoea and skin rash which should be treated symptomatically.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

Methotrexate supplied by pharmacy will be given as a single-dose intramuscular MTX (50mg/m2) injection as per standard care. SmPC in appendix 2.

6.7.2 Permitted Medications

Refer to SmPCs for gefitinib and methotrexate (Appendix 1 and 2).

6.7.3 Prohibited Medications for Gefitinib

Whilst there is no prohibited medication in combination with gefitinib, care should be taken with co-administration of the following drugs:

Rifampicin: avoid long course of rifampicin as dose of gefitinib may need to be increased.
Antacids: H2 antagonists and Proton Pump Inhibitors (PPIs), avoid co-administration with gefitinib as its absorption will be decreased. These should be taken two hours before taking the study medication or one hour after taking the study medication.
Phenytoin: may decrease gefitinib concentration and affect its efficacy.
Warfarin: increased INR and/or bleeding may occur; monitor INR regularly and decrease dose of warfarin if required.
St John's Wort: may reduce efficacy.

7 STUDY ASSESSMENTS

Study assessments prior to treatment:

As part of routine clinical practice, clinical assessment will have been carried out prior to approach into study to assess suitability for MTX treatment and therefore suitability for study. These parameters will be included and may be transcribed into CRF following consent:

- USS pelvis (transvaginal if necessary)
- Serum hCG(s) level (IU/L)
- Safety bloods (FBC, LFTS, U&Es)

- Height and weight to calculate BMI/BSA

Day of treatment study assessments:

- Consent
- Medical history
- Eligibility (confirmed by doctor)
- Randomisation to gefitinib or placebo
- Treatment allocated
- Case report forms completed

Participants will then follow standard clinical care as per their local protocol for the medical management of EP with MTX until day of resolution of the EP defined as serum hCG ≤15 IU/L or day of surgical treatment.

Study assessments:

These will follow the pattern of standard clinical care as per the local protocol for the medical management of EP with MTX. This may vary at each individual participating site. At each of these clinical visits the participant's clinical care team or member of the research team will complete a trial CRF which will include:

- Adverse events
- Compliance to treatment
- A question regarding whether they are happy to continue with the study

Safety assessment:

On or between follow up days 14 and 21, blood samples will be collected once to monitor FBC, U&Es and LFTs. If the result is out of the local trust range **and** is considered to be clinically significant, a clinician, on the GEM3 delegation log, should make a decision on any further action. The blood test should be repeated until the result returns to a level that is deemed no longer clinically significant. This will not be recorded as AE. (Day of MTX treatment is defined as either day 0 or day 1 depending on local policies).

Three months post-resolution (by telephone)

- Acceptability of treatment questions
- Return of menses question
- Requirement for surgery following hCG level ≤ 15 IU/L

7.1 SAFETY ASSESSMENTS

Safety assessments will be taken at baseline and throughout participation.

At baseline:

Full medical history to assess eligibility and pre-existing conditions (source documentation for this will be medical notes)
Clinical assessment
FBC, U&Es, LFTs

Each contact:
Open ended question to ascertain any AEs

Follow up: on or between day 14-21^

FBC, U&Es and LFTs

STUDY ASSESSMENTS

TABLE 1: Summary of Study Assessments

	Day of Treatment	Standard Clinical Care Visits	Day 14 – 21^ (during scheduled clinical care visits)	Month 3
Consent	✓	✓*	✓*	✓*
Clinical Assessment	✓	✓	✓	
Serum hCG (within 1 day)	✓	✓	✓	
FBC, U&Es, LFTs (#within 3 days of treatment)**	✓		✓	
Adverse Events		✓***	✓	
Compliance		✓		
Telephone consultation				✓

* ongoing consent will be confirmed at each visit

** until back to within normal ranges and stop date documented where applicable

*** if this clinical appointment falls when research staff are not available, the local research team will contact the participant at the earliest possible date to ascertain any AEs.
^ Sites will define day of MTX treatment as either day 0 or day 1 depending on local policies.

7.2 LONG TERM FOLLOW UP ASSESSMENTS

The future fertility of the participants in the GEM3 trial is of interest and we will now, as part of GEM3, contact participants between 12 months to 5 years post participation to determine their reproductive history following their ectopic pregnancy (collected once over this time period). This information may be

obtained via medical records or a short telephone call. Consent is asked for this on the ICF.

7.3 STORAGE AND ANALYSIS OF SAMPLES

All blood samples will be analysed in NHS accredited labs as per standard care.

8 DATA COLLECTION

The patient's clinical record will be considered to be source data, CRF and 3 month questionnaire. Information will be abstracted from the clinical record into the case report form (CRF). Data will be collected as it becomes available - i.e. at or shortly after each patient visit by members of the clinical team supported by research staff. Missing data will be kept to a minimum, and where possible will be collected from participants regardless of whether they have been compliant to their allocated treatment. We will collect reasons for missing data.

9 DATA MANAGEMENT

9.1 Personal Data

The following personal data will be collected as part of the research:
Name, hospital number, contact details (phone number and address)

Personal data will be stored by the local research teams at locked cabinets with limited access. The data collected will be anonymised.

Personal data will be stored for at least 5 years from the end of the study.

9.1.1 Transfer of Data

Personal data collected by the study will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).
Anonymised data collected or generated by the study may be shared with researchers at Sponsor organisations or at other organisations. These can be universities, NHS organisations or companies involved in health and care research.

9.1.2 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site)

9.1.3 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10 STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

The target sample size is 328 participants and is based on data taken from the Phase II study (GEM2), published cohort data (BMC Pregnancy Childbirth. 2013

13:30; Obstet Gynecol Int. 2014 2014:423708) and an audit of Edinburgh and Imperial of women undergoing usual care (2012; focusing on those participants with serum hCG >1000 IU/L). The cohort and audit data suggest a 30% rate of surgical intervention in the MTX group, with 15% expected in the gefitinib plus MTX group (actual figure from the phase II study was 14% but this has been conservatively rounded up). To detect this absolute difference in proportions of 15% with 90% power and an alpha error rate of 5%, a total of 322 participants would need to be randomised (161 per group). Assuming and adjusting for a 2% loss to follow-up rate, 328 participants need to be recruited.

10.2 PROPOSED ANALYSES

A separate Statistical Analysis Plan will provide a detailed description of the planned analyses. A brief outline is given below.

Point estimates and two-sided 95% confidence intervals will be calculated for all main outcome measures. P-values will be reported from two-sided tests at the 5% significance level for the primary outsome and SAEs only. All estimates will be adjusted for the minimisation variables listed (baseline hCG level, BMI, ectopic size and centre) in regression models where possible. Analysis will be of all randomised subjects in the intention to treat population.

10.2.1 PRIMARY OUTCOME ANALYSIS

The primary endpoint is surgical intervention for the treatment of EP. A log-binomial regression model will be used to calculate the relative risk and 95% confidence interval. The p-value from the associated chi-squared test will be produced and used to determine statistical significance.

10.2.2 SECONDARY OUTCOME ANALYSIS

The secondary endpoints are the need for further treatment with MTX, the number of days to resolution of the pregnancy (hCG ≤15 IU/L), the number of hospital visits associated with treatment, and patient satisfaction measured by a Likert scale. Dichotomous outcomes (e.g. need for additional treatment) will be analysed in the same fashion as the primary outcome. Time from randomisation to successful resolution will be analysed by log-rank test with a Cox Proportional Hazard (PH) model used to determine hazard ratios, if the assumptions of proportionality are met. Standard methods will be used to analyse other secondary outcomes.

10.2.3 MISSING DATA/SENSITIVITY ANALYSES

Every attempt will be made to collect all follow-up data on all participants (unless a participant withdraws consent for follow-up data collection).If a participant withdraws from treatment she will be followed up unless she specifically states otherwise. It is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis. This presents a risk of bias, and secondary sensitivity analyses will be undertaken to

assess the possible impact of the risk. This will include a worse-case assumption that those participants missing the primary outcome had surgery. Other sensitivity analyses will involve simulating missing responses using a multiple imputation (MI) approach.

10.2.4 SUBGROUP ANALYSES

Subgroup analyses will be limited to the same variables used in minimisation (baseline hCG level, BMI, ectopic size)with the exception of by centre, in the primary outcome only. . Tests for statistical heterogeneity will be performed through examination of the relevant interaction parameter in the regression model.

10.2.5 INTERIM ANALYSES

Interim analyses will be conducted on behalf of the DMC. These will be considered together with a full safety report including Serious Adverse Events. The DMC will meet before recruitment commences, and thereafter at least annually. Effectiveness and futility criteria will be ratified by the DMC; suggested stopping criteria are based on a pragmatic approach with further details given in section 12.3. The DAMOCLES charter will be adopted by the DMC and will include a specific remit for reviewing emerging data from other trials.

10.2.6 FINAL ANALYSIS

The primary analysis for the study will occur after all randomised participants have completed full follow-up (following the last 3 month post-resolution assessment) and all outcome data has been entered into the study database.

11 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the Summary of Product Characteristics (SmPC) Appendix 1.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after joining the trial must be recorded in detail in the Case Report Form (CRF) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

11.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation; (see exceptions in section 11.2);
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria but will be recorded in AE log. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

Adverse Events (AEs) for new malignant tumours reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the 'any other significant medical event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history, and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the relevant Summary of Product Characteristics (SmPC) Section 4.8 (Appendix 1).

11.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital or had any accidents. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

EXCEPTIONS

Events not to be recorded as AEs

The following known side effects of MTX and gefitinib will be noted on the CRF but not recorded as AEs - diarrhoea, nausea, vomiting, skin rash, increased ALTs (out with normal range), dizziness, mouth ulcers, fatigue ***unless meeting seriousness criteria of a SAE.***

Events not to be reported as SAEs

1. Admittance to hospital for surgery related to EP*
2. Admittance to hospital for monitoring of EP*
3. Admittance to hospital for monitoring of EP pain*
4. Admittance to hospital for elective treatment planned prior to enrolment**

*Hospitalisation for these events will not be reported as a SAE as this is an expected event within this population group and will not be recorded as an AE.

**This event should be recorded on the AE log.

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until resolution - hCG level ≤15 IU/L or date of surgery for treatment of EP ie, AEs and SAEs will not be collected from resolution to follow-up phone call at 3 months.

11.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity, causality, date of resolution as well as treatment required, investigations needed and outcome.

11.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and SARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

For randomised double blind studies, AEs will be assessed as though the participant is taking active IMP. SUSARs will be unblinded by ACCORD before they are reported to REC and CA (by ACCORD).

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

11.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

11.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.

- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. Delete Investigators Brochure/Summary of Product Characteristics as appropriate to the information available for the IMP. State the specific section of the document that contains the reference safety information i.e. known undesirable effects. Standard SmPCs have this information in section 4.8.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

11.4.3 Assessment of Expectedness

If an event is judged to be an SAR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented Section 4.8 of the SmPC (Appendix 1).

The event may be classed as either:

Expected: the SAR is consistent with the toxicity of the IMP listed in the SmPC.

Unexpected: the SAR is not consistent with the toxicity in the SmPC.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety@Accord.Scot. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

Onward reporting.

The GEM3 trial management team should be notified of any SAEs/SARs/SUSARs by emailing gem3@ed.ac.uk.

Astra Zeneca should be notified of any SAEs/SARs/SUSARs by faxing 46 31 776 37 34 or emailing AEmailboxclinicaltrialTCS@astrazeneca.com within 15 days of the notification to the Sponsor.

The DMC will be notified of any SAEs and SUSARs that are related to the IMP at the time of every meeting.

11.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD, unless otherwise delegated will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

11.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

12 PREGNANCY

Not applicable but conception should be avoided by using effective contraception for at least 3 months following administration of last dose of MTX.

13 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager, senior trials coordinator and coordinating nurses.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The GEM3 trial management team will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators and the sponsor on all aspects of the trial and affording protection for participants by ensuring the trial is conducted according to the guidelines for Good Clinical Practice.

13.3 DATA MONITORING COMMITTEE

If the Gefitinib and MTX differs from MTX alone with respect to the primary or major secondary outcome, then this may become apparent before the target recruitment has been reached. Similarly, new evidence might emerge from other sources that Gefitinib and MTX differs in its effectiveness compared with MTX alone. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring Committee (DMC) along with updates on results of other related studies, and any other analyses that the DMC may request.

The DMC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $p<0.001$ (similar to Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

The DMC will be convened and operate according to the recommendations arising from the DAMOCLES project. A trial specific charter will be drawn up to define the remit and terms of reference of the DMC, which will be agreed by the Chief Investigator and the DMC members before the commencement of the study.

13.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

13.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions (delete if no adaptations were possible) could be incorporated into to trial design.

13.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and central monitoring activities as necessary (delete where not required). ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

14 GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).
Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

14.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

14.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

14.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified

delegated person and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

14.3.2 Study Site Staff

The Principal Investigator must be familiar with the IMP, protocol and the study requirements. It is the Principal Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

14.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF. All data will be transferred to a bespoke database which will be created by BCTU.

14.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to BCTU and the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

14.3.5 GCP Training

All staff involved in the study must hold evidence of appropriate GCP or targeted GCP training.

14.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information. Access to personal information will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

15 STUDY CONDUCT RESPONSIBILITIES

15.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

15.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.

15.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

15.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

15.5 END OF STUDY

The end of study is defined as following the last 3 month post resolution assessment.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

15.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY – N/A

15.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

16 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

16.2 PUBLICATION

The clinical study report will be submitted to the competent authority (ies) within 1 year of the end of the study. A copy must also be submitted to ACCORD.

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion) and a copy made available to the DMEC.

16.3 PEER REVIEW

This trial was externally peer reviewed by the NIHR.

APPENDIX 1: Summary of Product Characteristics – Gefitinib

17 Iressa 250mg film-coated tablets

Summary of Product Characteristics Updated 02-May-2018 | AstraZeneca UK Limited

1. Name of the medicinal product

IRESSA 250 mg film-coated tablets

2. Qualitative and quantitative composition

Each tablet contains 250 mg of gefitinib.

Excipients with known effect:

Each tablet contains 163.5 mg of lactose (as monohydrate).

Each tablet contains 3.86 mg of sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets (tablet).

Tablets are brown, round, biconvex, impressed with “IRESSA 250” on one side and plain on the other.

4. Clinical particulars

4.1 Therapeutic indications

IRESSA is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see section 4.4).

4.2 Posology and method of administration

Treatment with IRESSA should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.

Posology

The recommended posology of IRESSA is one 250 mg tablet once a day. If a dose is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

Paediatric population

The safety and efficacy of IRESSA in children and adolescents aged less than 18 years have not been established. There is no relevant use of gefitinib in the paediatric population in the indication of NSCLC.

Hepatic impairment

Patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to cirrhosis have increased plasma concentrations of gefitinib. These patients should be closely monitored for adverse events. Plasma concentrations were not increased in patients with elevated aspartate transaminase (AST), alkaline phosphatase or bilirubin due to liver metastases (see section 5.2).

Renal impairment

No dose adjustment is required in patients with impaired renal function at creatinine clearance >20 ml/min. Only limited data are available in patients with creatinine clearance ≤ 20 ml/min and caution is advised in these patients (see section 5.2).

Elderly

No dose adjustment is required on the basis of patient age (see section 5.2).
CYP2D6 poor metabolisers
No specific dose adjustment is recommended in patients with known CYP2D6 poor metaboliser genotype, but these patients should be closely monitored for adverse events (see section 5.2).
Dose adjustment due to toxicity
Patients with poorly tolerated diarrhoea or skin adverse reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose (see section 4.8). For patients unable to tolerate treatment after a therapy interruption, gefitinib should be discontinued and an alternative treatment should be considered.
Method of administration
The tablet may be taken orally with or without food, at about the same time each day. The tablet can be swallowed whole with some water or if dosing of whole tablets is not possible, tablets may be administered as a dispersion in water (non-carbonated). No other liquids should be used. Without crushing it, the tablet should be dropped in half a glass of drinking water. The glass should be swirled occasionally, until the tablet is dispersed (this may take up to 20 minutes). The dispersion should be drunk immediately after dispersion is complete (i.e. within 60 minutes). The glass should be rinsed with half a glass of water, which should also be drunk. The dispersion can also be administered through a naso-gastric or gastrostomy tube.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

When considering the use of IRESSA as a treatment for locally advanced or metastatic NSCLC, it is important that EGFR mutation assessment of the tumour tissue is attempted for all patients. If a tumour sample is not evaluable, then circulating tumour DNA (ctDNA) obtained from a blood (plasma) sample may be used.
Only robust, reliable and sensitive test(s) with demonstrated utility for the determination of EGFR mutation status of tumours or ctDNA should be used to avoid false negative or false positive determinations (see section 5.1).
Interstitial lung disease (ILD)
Interstitial lung disease (ILD), which may be acute in onset, has been observed in 1.3% of patients receiving gefitinib, and some cases have been fatal (see section 4.8). If patients experience worsening of respiratory symptoms such as dyspnoea, cough and fever, IRESSA should be interrupted and the patient should be promptly investigated. If ILD is confirmed, IRESSA should be discontinued and the patient treated appropriately.
In a Japanese pharmacoepidemiological case control study in 3159 patients with NSCLC receiving gefitinib or chemotherapy who were followed up for 12 weeks, the following risk factors for developing ILD (irrespective of whether the patient received IRESSA or chemotherapy) were identified: smoking, poor performance status (PS ≥ 2), CT scan evidence of reduced normal lung (≤ 50%), recent diagnosis of NSCLC (< 6 months), pre-existing ILD, older age (≥ 55 years old) and concurrent cardiac disease. An increased risk of ILD on gefitinib relative to chemotherapy was seen predominantly during the first 4 weeks of treatment (adjusted OR 3.8; 95% CI 1.9 to 7.7); thereafter the relative risk was lower

(adjusted OR 2.5; 95% CI 1.1 to 5.8). Risk of mortality among patients who developed ILD on IRESSA or chemotherapy was higher in patients with the following risk factors: smoking, CT scan evidence of reduced normal lung (≤ 50%), pre-existing ILD, older age (≥ 65 years old), and extensive areas adherent to pleura (≥ 50%).

Hepatotoxicity and liver impairment

Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, bilirubin) have been observed, uncommonly presenting as hepatitis (see section 4.8). There have been isolated reports of hepatic failure which in some cases led to fatal outcomes. Therefore, periodic liver function testing is recommended. Gefitinib should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe.

Impaired liver function due to cirrhosis has been shown to lead to increased plasma concentrations of gefitinib (see section 5.2).

Interactions with other medicinal products

CYP3A4 inducers may increase metabolism of gefitinib and decrease gefitinib plasma concentrations. Therefore, concomitant administration of CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St John's wort/*Hypericum perforatum*) may reduce efficacy of the treatment and should be avoided (see section 4.5).

In individual patients with CYP2D6 poor metaboliser genotype, treatment with a potent CYP3A4 inhibitor might lead to increased plasma levels of gefitinib. At initiation of treatment with a CYP3A4 inhibitor, patients should be closely monitored for gefitinib adverse reactions (see section 4.5).

International normalised ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin together with gefitinib (see section 4.5). Patients taking warfarin and gefitinib concomitantly should be monitored regularly for changes in prothrombin time (PT) or INR.

Medicinal products that cause significant sustained elevation in gastric pH, such as proton-pump inhibitors and h_2-antagonists may reduce bioavailability and plasma concentrations of gefitinib and, therefore, may reduce efficacy. Antacids if taken regularly close in time to administration of gefitinib may have a similar effect (see sections 4.5 and 5.2).

Data from phase II clinical trials, where gefitinib and vinorelbine have been used concomitantly, indicate that gefitinib may exacerbate the neutropenic effect of vinorelbine.

Lactose

IRESSA contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

IRESSA contains less than 1 mmol (23 mg) of sodium per tablet, that is to say it is essentially 'sodium-free'.

Further precautions for use

Patients should be advised to seek medical advice immediately if they experience severe or persistent diarrhoea, nausea, vomiting or anorexia as these may indirectly lead to dehydration. These symptoms should be managed as clinically indicated (see section 4.8).

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision,

eye pain and/or red eye should be referred promptly to an ophthalmology specialist.
If a diagnosis of ulcerative keratitis is confirmed, treatment with gefitinib should be interrupted, and if symptoms do not resolve, or if symptoms recur on reintroduction of gefitinib, permanent discontinuation should be considered.
In a phase I/II trial studying the use of gefitinib and radiation in paediatric patients, with newly diagnosed brain stem glioma or incompletely resected supratentorial malignant glioma, 4 cases (1 fatal) of Central Nervous System (CNS) haemorrhages were reported from 45 patients enrolled. A further case of CNS haemorrhage has been reported in a child with an ependymoma from a trial with gefitinib alone. An increased risk of cerebral haemorrhage in adult patients with NSCLC receiving gefitinib has not been established.
Gastrointestinal perforation has been reported in patients taking gefitinib. In most cases this is associated with other known risk factors, including concomitant medications such as steroids or NSAIDs, underlying history of GI ulceration, age, smoking or bowel metastases at sites of perforation.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of gefitinib is via the cytochrome P450 isoenzyme CYP3A4 (predominantly) and via CYP2D6.

Active substances that may increase gefitinib plasma concentrations

In vitro studies have shown that gefitinib is a substrate of p-glycoprotein (Pgp). Available data do not suggest any clinical consequences to this *in vitro* finding.
Substances that inhibit CYP3A4 may decrease the clearance of gefitinib. Concomitant administration with potent inhibitors of CYP3A4 activity (e.g. ketoconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin, telithromycin) may increase gefitinib plasma concentrations. The increase may be clinically relevant since adverse reactions are related to dose and exposure. The increase might be higher in individual patients with CYP2D6 poor metaboliser genotype. Pre-treatment with itraconazole (a potent CYP3A4 inhibitor) resulted in an 80% increase in the mean AUC of gefitinib in healthy volunteers. In situations of concomitant treatment with potent inhibitors of CYP3A4 the patient should be closely monitored for gefitinib adverse reactions.
There are no data on concomitant treatment with an inhibitor of CYP2D6 but potent inhibitors of this enzyme might cause increased plasma concentrations of gefitinib in CYP2D6 extensive metabolisers by about 2-fold (see section 5.2). If concomitant treatment with a potent CYP2D6 inhibitor is initiated, the patient should be closely monitored for adverse reactions.

Active substances that may reduce gefitinib plasma concentrations

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease gefitinib plasma concentrations and thereby reduce the efficacy of gefitinib. Concomitant medicinal products that induce CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or St John's wort, *Hypericum perforatum*)), should be avoided. Pre-treatment with rifampicin (a potent CYP3A4 inducer) in healthy volunteers reduced mean gefitinib AUC by 83% (see section 4.4).
Substances that cause significant sustained elevation in gastric pH may reduce gefitinib plasma concentrations and thereby reduce the efficacy of gefitinib. High doses of short-acting antacids may have a similar effect if taken regularly close in time to administration of gefitinib. Concomitant administration of gefitinib with ranitidine at a dose that caused sustained elevations in gastric pH ≥ 5 resulted in

a reduced mean gefitinib AUC by 47% in healthy volunteers (see sections 4.4 and 5.2).

Active substances that may have their plasma concentrations altered by gefitinib

In vitro studies have shown that gefitinib has limited potential to inhibit CYP2D6. In a clinical trial in patients, gefitinib was co-administered with metoprolol (a CYP2D6 substrate). This resulted in a 35% increase in exposure to metoprolol. Such an increase might potentially be relevant for CYP2D6 substrates with narrow therapeutic index. When the use of CYP2D6 substrates are considered in combination with gefitinib, a dose modification of the CYP2D6 substrate should be considered especially for products with a narrow therapeutic window.

Gefitinib inhibits the transporter protein BCRP *in vitro*, but the clinical relevance of this finding is unknown.

Other potential interactions

INR elevations and/or bleeding events have been reported in some patients concomitantly taking warfarin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must be advised not to get pregnant during therapy.

Pregnancy

There are no data from the use of gefitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IRESSA should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether gefitinib is secreted in human milk. Gefitinib and metabolites of gefitinib accumulated in milk of lactating rats (see section 5.3). Gefitinib is contraindicated during breast-feeding and therefore breast-feeding must be discontinued while receiving gefitinib therapy (see section 4.3).

4.7 Effects on ability to drive and use machines

During treatment with gefitinib, asthenia has been reported. Therefore, patients who experience this symptom should be cautious when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In the pooled dataset from the ISEL, INTEREST and IPASS phase III clinical trials (2462 IRESSA-treated patients), the most frequently reported adverse drug reactions (ADRs), occurring in more than 20% of the patients, are diarrhoea and skin reactions (including rash, acne, dry skin and pruritus). ADRs usually occur within the first month of therapy and are generally reversible. Approximately 8% of patients had a severe ADR (common toxicity criteria (CTC) grade 3 or 4). Approximately 3% of patients stopped therapy due to an ADR.

Interstitial lung disease (ILD) has occurred in 1.3% of patients, often severe (CTC grade 3-4). Cases with fatal outcomes have been reported.

Tabulated list of adverse reactions

The safety profile presented in Table 1 is based on the gefitinib clinical development programme and postmarketed experience. Adverse reactions have been assigned to the frequency categories in Table 1 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the ISEL, INTEREST and IPASS phase III clinical trials (2462 IRESSA-treated patients).

Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions

Adverse reactions by system organ class and frequency		
Metabolism and nutrition disorders	Very common	Anorexia mild or moderate (CTC grade 1 or 2)
Eye disorders	Common	Conjunctivitis, blepharitis, and dry eye*, mainly mild (CTC grade 1)
	Uncommon	Corneal erosion, reversible and sometimes in association with aberrant eyelash growth
		Keratitis (0.12%)
Vascular disorders	Common	Haemorrhage, such as epistaxis and haematuria
Respiratory, thoracic and mediastinal disorders	Common	Interstitial lung disease (1.3%), often severe (CTC grade 3-4). Cases with fatal outcomes have been reported
Gastrointestinal disorders	Very common	Diarrhoea, mainly mild or moderate (CTC grade 1 or 2)
		Vomiting, mainly mild or moderate (CTC grade 1 or 2)
		Nausea, mainly mild (CTC grade 1)
		Stomatitis, predominantly mild in nature (CTC grade 1)
	Common	Dehydration, secondary to diarrhoea, nausea, vomiting or anorexia
		Dry mouth*, predominantly mild (CTC grade 1)
	Uncommon	Pancreatitis.
		Gastrointestinal perforation
Hepatobiliary disorders	Very common	Elevations in alanine aminotransferase, mainly mild to moderate
	Common	Elevations in aspartate aminotransferase, mainly mild to moderate
		Elevations in total bilirubin, mainly mild to moderate
	Uncommon	Hepatitis**
Skin and subcutaneous tissue disorders	Very common	Skin reactions, mainly a mild or moderate (CTC grade 1 or 2) pustular rash, sometimes itchy with dry skin, including skin fissures, on an erythematous base
	Common	Nail disorder
		Alopecia
		Allergic reactions (1.1%), including angioedema and

		urticaria
	Rare	Bullous conditions including toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme
		Cutaneous vasculitis
Renal and urinary disorders	Common	Asymptomatic laboratory elevations in blood creatinine
		Proteinuria
		Cystitis
	Rare	Haemorrhagic cystitis
General disorders and administration site conditions	Very common	Asthenia, predominantly mild (CTC grade 1)
	Common	Pyrexia

The frequency of adverse drug reactions relating to abnormal laboratory values is based on patients with a change from baseline of 2 or more CTC grades in the relevant laboratory parameters.
*This adverse reaction can occur in association with other dry conditions (mainly skin reactions) seen with gefitinib.
**This includes isolated reports of hepatic failure which in some cases led to fatal outcomes.
Interstitial lung disease (ILD)
In the INTEREST trial, the incidence of ILD type events was 1.4% (10) patients in the gefitinib group *versus* 1.1% (8) patients in the docetaxel group. One ILD-type event was fatal, and this occurred in a patient receiving gefitinib.
In the ISEL trial, the incidence of ILD-type events in the overall population was approximately 1% in both treatment arms. The majority of ILD-type events reported was from patients of Asian ethnicity and the ILD incidence among patients of Asian ethnicity receiving gefitinib therapy and placebo was approximately 3% and 4% respectively. One ILD-type event was fatal, and this occurred in a patient receiving placebo.
In a post-marketing surveillance study in Japan (3350 patients) the reported rate of ILD-type events in patients receiving gefitinib was 5.8%. The proportion of ILD-type events with a fatal outcome was 38.6%.
In a phase III open-label clinical trial (IPASS) in 1217 patients comparing IRESSA to carboplatin/paclitaxel doublet chemotherapy as first-line treatment in selected patients with advanced NSCLC in Asia, the incidence of ILD-type events was 2.6% on the IRESSA treatment arm versus 1.4% on the carboplatin/paclitaxel treatment arm.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
UK
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store
Ireland
HPRA Pharmacovigilance

Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie
Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

There is no specific treatment in the event of overdose of gefitinib. However, in phase I clinical trials, a limited number of patients were treated with daily doses of up to 1000 mg. An increase of frequency and severity of some adverse reactions was observed, mainly diarrhoea and skin rash. Adverse reactions associated with overdose should be treated symptomatically; in particular severe diarrhoea should be managed as clinically indicated. In one study a limited number of patients were treated weekly with doses from 1500 mg to 3500 mg**.** In this study IRESSA exposure did not increase with increasing dose, adverse events were mostly mild to moderate in severity, and were consistent with the known safety profile of IRESSA.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01XE02

Mechanism of action and pharmacodynamic effects

The epidermal growth factor (EGF) and its receptor (EGFR [HER1; ErbB1]) have been identified as key drivers in the process of cell growth and proliferation for normal and cancer cells. EGFR activating mutation within a cancer cell is an important factor in promotion of tumour cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of metastasis.

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase and is an effective treatment for patients with tumours with activating mutations of the EGFR tyrosine kinase domain regardless of line of therapy. No clinically relevant activity has been shown in patients with known EGFR mutation-negative tumours.

The common EGFR activating mutations (Exon 19 deletions; L858R) have robust response data supporting sensitivity to gefitinib; for example a progression free survival HR (95% CI) of 0.489 (0.336, 0.710) for gefitinib vs. doublet chemotherapy [WJTOG3405]. Gefitinib response data is more sparse in patients whose tumours contain the less common mutations; the available data indicates that G719X, L861Q and S7681 are sensitising mutations; and T790M alone or exon 20 insertions alone are resistance mechanisms.

Resistance

Most NSCLC tumours with sensitising EGFR kinase mutations eventually develop resistance to IRESSA treatment, with a median time to disease progression of 1 year. In about 60% of cases, resistance is associated with a secondary T790M mutation for which T790M targeted EGFR TKIs may be considered as a next line treatment option. Other potential mechanisms of resistance that have been reported following treatment with EGFR signal blocking agents include: bypass signalling such as HER2 and MET gene amplification and PIK3CA mutations.

Phenotypic switch to small cell lung cancer has also been reported in 5-10% of cases.

Circulating Tumour DNA (ctDNA)

In the IFUM trial, mutation status was assessed in tumour and ctDNA samples derived from plasma, using the Therascreen EGFR RGQ PCR kit (Qiagen). Both ctDNA and tumour samples were evaluable for 652 patients out of 1060 screened. The objective response rate (ORR) in those patients who were tumour and ctDNA mutation positive was 77% (95% CI: 66% to 86%) and in those who were tumour only mutation positive 60% (95% CI: 44% to 74%).

Table 2 Summary of baseline mutation status for tumour and ctDNA samples in all screened patients evaluable for both samples

Measure	**Definition**	**IFUM rate % (CI)**	**IFUM N**
Sensitivity	Proportion of tumour M+ that are M+ by ctDNA	65.7 (55.8, 74.7)	105
Specificity	Proportion of tumour M- that are M- by ctDNA)	99.8 (99.0, 100.0)	547

These data are consistent with the pre-planned exploratory Japanese subgroup analysis in IPASS (Goto 2012). In that study ctDNA derived from serum, not plasma was used for EGFR mutation analysis using the EGFR Mutation Test Kit (DxS) (N= 86). In that study, sensitivity was 43.1%, specificity was 100%.

Clinical efficacy and safety

First line treatment

The randomised phase III first line IPASS study was conducted in patients in Asia[1] with advanced (stage IIIB or IV) NSCLC of adenocarcinoma histology who were ex-light smokers (ceased smoking ≥ 15 years ago and smoked ≤ 10 pack years) or never smokers (see Table 3).

[1]China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan and Thailand.

Table 3 Efficacy outcomes for gefitinib versus carboplatin/paclitaxel from the IPASS study

Population	**N**	**Objective response rates and 95% CI for difference between treatments[a]**	**Primary endpoint Progression free survival** (PFS)[a]2[b]	**Overall survival[ab]**
Overall	1217	43.0% vs 32.2% [5.3%, 16.1%]	HR 0.74 [0.65, 0.85] 5.7 m vs 5.8 m p<0.0001	HR 0.90 [0.79, 1.02] 18.8 m vs 17. 4m p=0.1087
EGFR mutation-positive	261	71.2% vs 47.3% [12.0%, 34.9%]	HR 0.48 [0.36, 0.64] 9.5 m vs 6.3 m p<0.0001	HR 1.00 [0.76, 1.33] 21.6 m vs 21.9 m

EGFR mutation-negative	176	1.1% vs 23.5% [-32.5%, -13.3%]	HR 2.85 [2.05, 3.98] 1.5 m vs 5.5 m p<0.0001	HR 1.18 [0.86, 1.63] 11.2 m vs 12.7 m
EGFR mutation-unknown	780	43.3% vs 29.2% [7.3%, 20.6%]	HR 0.68 [0.58 to 0.81] 6.6 m vs 5.8 m p<0.0001	HR 0.82 [0.70 to 0.96] 18.9 m vs. 17.2 m

a Values presented are for IRESSA versus carboplatin/paclitaxel.
b "m" is medians in months. Numbers in square brackets are 95% confidence intervals for HR
N Number of patients randomised.
HR Hazard ratio (hazard ratios <1 favour IRESSA)

Quality of life outcomes differed according to EGFR mutation status. In EGFR mutation-positive patients, significantly more IRESSA-treated patients experienced an improvement in quality of life and lung cancer symptoms vs. carboplatin/paclitaxel (see Table 4).

Table 4 Quality of life outcomes for gefitinib versus carboplatin/paclitaxel from the IPASS study

Population	**N**	**FACT-L QoL improvement rate [a] %**	**LCS symptom improvement rate [a]%**
Overall	1151	(48.0% vs 40.8%) p=0.0148	(51.5% vs 48.5%) p=0.3037
EGFR mutation-positive	259	(70.2% vs 44.5%) p<0.0001	(75.6% vs 53.9%) p=0.0003
EGFR mutation-negative	169	(14.6% vs 36.3%) p=0.0021	(20.2% vs 47.5%) p=0.0002

Trial outcome index results were supportive of FACT-L and LCS results
[a] Values presented are for IRESSA versus carboplatin/paclitaxel.
N Number of patients evaluable for quality of life analyses
QoL Quality of life
FACT-L Functional assessment of cancer therapy-lung
LCS Lung cancer subscale

In the IPASS trial, IRESSA demonstrated superior PFS, ORR, QoL and symptom relief with no significant difference in overall survival compared to carboplatin/paclitaxel in previously untreated patients, with locally advanced or metastatic NSCLC, whose tumours harboured activating mutations of the EGFR tyrosine kinase.

Pretreated patients

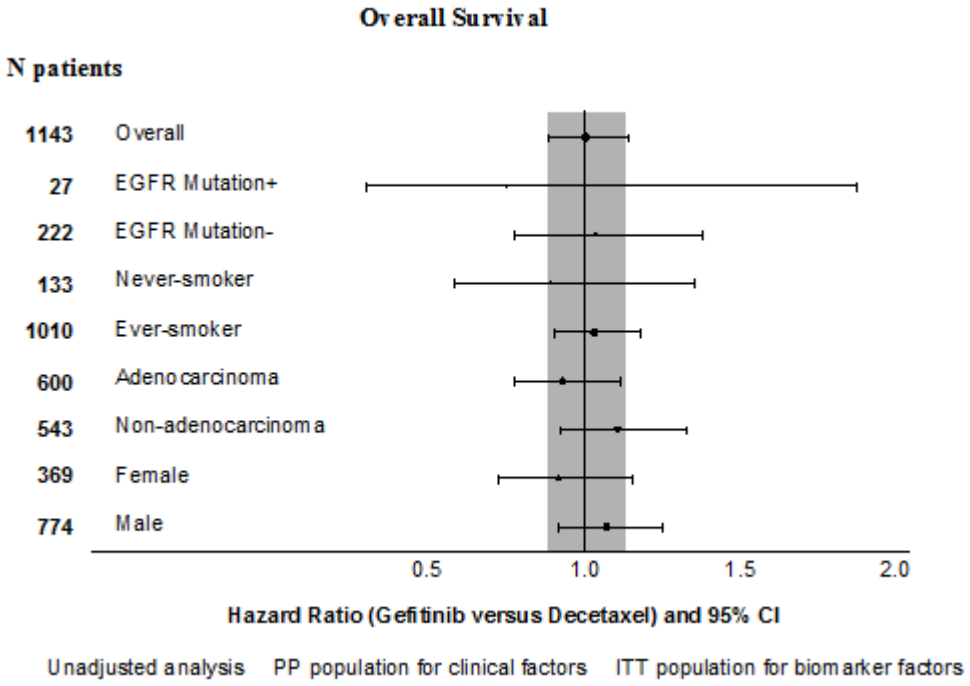
The randomised phase III INTEREST study was conducted in patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy. In the overall population, no statistically significant difference between gefitinib and docetaxel (75 mg/m^2) was observed for overall survival, progression free survival and objective response rates (see Table 5).

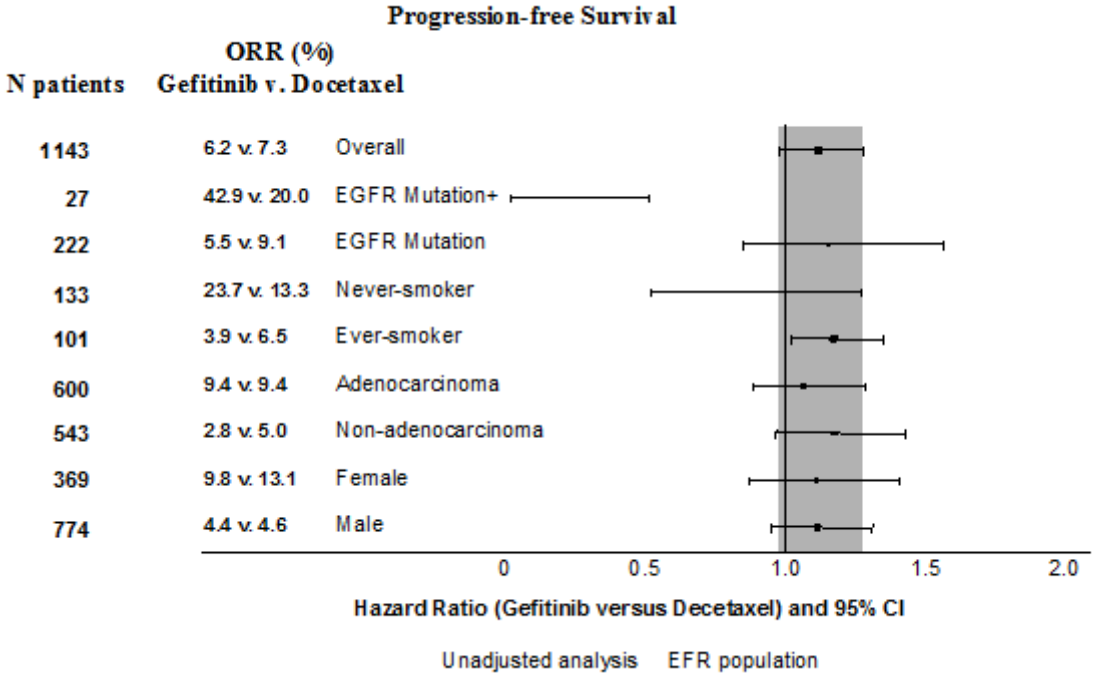
Table 5 Efficacy outcomes for gefitinib versus docetaxel from the INTEREST study

Population	N	Objective response rates and 95% CI for difference between treatments[a]	Progression free survival[ab]	Primary endpoint overall survival[ab]
Overall	1466	9.1% vs 7.6% [-1.5%, 4.5%]	HR 1.04 [0.93, 1.18] 2.2 m vs 2.7 m p=0.4658	HR 1.020 [0.905, 1.150] [c] 7.6 m vs 8.0 m p=0.7332
EGFR mutation-positive	44	42.1% vs 21.1% [-8.2%, 46.0%]	HR 0.16 [0.05, 0.49] 7.0 m vs 4.1 m p=0.0012	HR 0.83 [0.41, 1.67] 14.2 m vs 16.6 m p=0.6043
EGFR mutation-negative	253	6.6% vs 9.8% [-10.5%, 4.4%]	HR 1.24 [0.94, 1.64] 1.7 m vs 2.6 m p=0.1353	HR 1.02 [0.78, 1.33] 6.4 m vs 6.0 m p=0.9131
Asians[c]	323	19.7% vs 8.7% [3.1%, 19.2%]	HR 0.83 [0.64, 1.08] 2.9 m vs 2.8 m p=0.1746	HR 1.04 [0.80, 1.35] 10.4 m vs 12.2 m p=0.7711
Non-Asians	1143	6.2% vs 7.3% [-4.3%, 2.0%]	HR 1.12 [0.98, 1.28] 2.0 m vs 2.7 m p=0.1041	HR 1.01 [0.89, 1.14] 6.9 m vs 6.9 m p=0.9259

a Values presented are for IRESSA versus docetaxel.
b “m” is medians in months. Numbers in square brackets are 96% confidence interval for overall survival HR in the overall population, or otherwise 95% confidence intervals for HR
c Confidence interval entirely below non-inferiority margin of 1.154
N Number of patients randomised.
HR Hazard ratio (hazard ratios <1 favour IRESSA)

Figures 1 and 2 Efficacy outcomes in subgroups of non-Asian patients in the INTEREST study
(N patients = Number of patients randomised)





The randomised phase III ISEL study, was conducted in patients with advanced NSCLC who had received 1 or 2 prior chemotherapy regimens and were refractory or intolerant to their most recent regimen. Gefitinib plus best supportive care was compared to placebo plus best supportive care. IRESSA did not prolong survival in the overall population. Survival outcomes differed by smoking status and ethnicity (see Table 6).

Table 6 Efficacy outcomes for gefitinib versus placebo from the ISEL study

Population	N	Objective response rates and 95% CI for difference between treatments[a]	Time to treatment failure[ab]	Primary endpoint overall survival[abc]
Overall	1692	8.0% vs 1.3% [4.7%, 8.8%]	HR 0.82 [0.73, 0.92] 3.0 m vs 2.6 m p=0.0006	HR 0.89 [0.77, 1.02] 5.6 m vs 5.1 m p=0.0871
EGFR mutation-positive	26	37.5% vs 0% [-15.1%, 61.4%]	HR 0.79 [0.20, 3.12] 10.8 m vs 3.8m p=0.7382	HR NC NR vs 4.3 m
EGFR mutation-negative	189	2.6% vs 0% [-5.6%, 7.3%]	HR 1.10 [0.78, 1.56] 2.0 m vs 2.6 m p=0.5771	HR 1.16 [0.79, 1.72] 3.7 m vs 5.9 m p=0.4449
Never smoker	375	18.1% vs 0% [12.3%, 24.0%]	HR 0.55 [0.42, 0.72] 5.6 m vs 2.8 m p<0.0001	HR 0.67 [0.49, 0.92] 8.9 m vs 6.1 m p=0.0124
Ever smoker	1317	5.3% vs 1.6% [1.4%, 5.7%]	HR 0.89 [0.78, 1.01] 2.7 m vs 2.6 m p=0.0707	HR 0.92 [0.79, 1.06] 5.0 m vs 4.9 m p=0.2420
Asians[d]	342	12.4% vs 2.1% [4.0%, 15.8%]	HR 0.69 [0.52, 0.91] 4.4 m vs 2.2 m p=0.0084	HR 0.66 [0.48, 0.91] 9.5 m vs 5.5 m p=0.0100
Non-Asians	1350	6.8% vs 1.0% [3.5%, 7.9%]	HR 0.86 [0.76, 0.98] 2.9 m vs 2.7 m p=0.0197	HR 0.92 [0.80, 1.07] 5.2 m vs 5.1 m p=0.2942

a Values presented are for IRESSA versus placebo.
b “m” is medians in months. Numbers in square brackets are 95% confidence intervals for HR
c Stratified log-rank test for overall; otherwise cox proportional hazards model
d Asian ethnicity excludes patients of Indian origin and refers to the racial origin of a patient group and not necessarily their place of birth
N Number of patients randomised
NC Not calculated for overall survival HR as the number of events is too few
NR Not reached
HR Hazard ratio (hazard ratios <1 favour IRESSA)
The IFUM study was a single-arm, multicentre study conducted in Caucasian patients (n=106) with activating, sensitising EGFR mutation positive NSCLC to confirm that the activity of gefitinib is similar in Caucasian and Asian populations.

The ORR according to investigator review was 70% and the median PFS was 9.7 months. These data are similar to those reported in the IPASS study.

EGFR mutation status and clinical characteristics

Clinical characteristics of never smoker, adenocarcinoma histology, and female gender have been shown to be independent predictors of positive EGFR mutation status in a multivariate analysis of 786 Caucasian patients from gefitinib studies* (see Table 7). Asian patients also have a higher incidence of EGFR mutation-positive tumours.

Table 7 Summary of multivariate logistic regression analysis to identify factors that independently predicted for the presence of EGFR mutations in 786 Caucasian patients*

Factors that predicted for presence of EGFR mutation	**p-value**	**Odds of EGFR mutation**	**Positive predictive value (9.5% of the overall population are EGFR mutation-positive (M+))**
Smoking status	<0.0001	6.5 times higher in never smokers than ever-smokers	28/70 (40%) of never smokers are M+ 47/716 (7%) of ever smokers are M+
Histology	<0.0001	4.4 times higher in adenocarcinoma than in non-adenocarcinoma	63/396 (16%) of patients with adenocarcinoma histology are M+ 12/390 (3%) of patients with non-adenocarcinoma histology are M+
Gender	0.0397	1.7 times higher in females than males	40/235 (17%) of females are M+ 35/551 (6%) of males are M+

*from the following studies: INTEREST, ISEL, INTACT 1&2, IDEAL 1&2, INVITE

5.2 Pharmacokinetic properties

Absorption

Following oral administration of gefitinib, absorption is moderately slow and peak plasma concentrations of gefitinib typically occur at 3 to 7 hours after administration. Mean absolute bioavailability is 59% in cancer patients. Exposure to gefitinib is not significantly altered by food. In a trial in healthy volunteers where gastric pH was maintained above pH 5, gefitinib exposure was reduced by 47%, likely due to impaired solubility of gefitinib in the stomach (see sections 4.4 and 4.5).

Distribution

Gefitinib has a mean steady-state volume of distribution of 1400 l indicating extensive distribution into tissue. Plasma protein binding is approximately 90%. Gefitinib binds to serum albumin and alpha 1-acid glycoprotein.

In vitro data indicate that gefitinib is a substrate for the membrane transport protein Pgp.

Biotransformation

In vitro data indicate that CYP3A4 and CYP2D6 are the major P450 isozyme involved in the oxidative metabolism of gefitinib.

In vitro studies have shown that gefitinib has limited potential to inhibit CYP2D6. Gefitinib shows no enzyme induction effects in animal studies and no significant inhibition (*in vitro*) of any other cytochrome P450 enzyme.
Gefitinib is extensively metabolised in humans. Five metabolites have been fully identified in excreta and 8 metabolites in plasma. The major metabolite identified was O-desmethyl gefitinib, which is 14-fold less potent than gefitinib at inhibiting EGFR stimulated cell growth and has no inhibitory effect on tumour cell growth in mice. It is therefore considered unlikely that it contributes to the clinical activity of gefitinib.
The formation of O-desmethyl gefitinib has been shown, *in vitro*, to be via CYP2D6. The role of CYP2D6 in the metabolic clearance of gefitinib has been evaluated in a clinical trial in healthy volunteers genotyped for CYP2D6 status. In poor metabolisers no measurable levels of O-desmethyl gefitinib were produced. The levels of exposure to gefitinib achieved in both the extensive and the poor metaboliser groups were wide and overlapping but the mean exposure to gefitinib was 2-fold higher in the poor metaboliser group. The higher average exposures that could be achieved by individuals with no active CYP2D6 may be clinically relevant since adverse effects are related to dose and exposure.
Elimination
Gefitinib is excreted mainly as metabolites via the faeces, with renal elimination of gefitinib and metabolites accounting for less than 4% of the administered dose. Gefitinib total plasma clearance is approximately 500 ml/min and the mean terminal half-life is 41 hours in cancer patients. Administration of gefitinib once daily results in 2- to 8-fold accumulation, with steady-state exposures achieved after 7 to 10 doses. At steady-state, circulating plasma concentrations are typically maintained within a 2- to 3-fold range over the 24-hour dosing interval.
Special populations
From analyses of population pharmacokinetic data in cancer patients, no relationships were identified between predicted steady-state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance (above 20 ml/min).
Hepatic impairment
In a phase I open-label study of single dose gefitinib 250 mg in patients with mild, moderate or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification), there was an increase in exposure in all groups compared with healthy controls. An average 3.1-fold increase in exposure to gefitinib in patients with moderate and severe hepatic impairment was observed. None of the patients had cancer, all had cirrhosis and some had hepatitis. This increase in exposure may be of clinical relevance since adverse experiences are related to dose and exposure to gefitinib.
Gefitinib has been evaluated in a clinical trial conducted in 41 patients with solid tumours and normal hepatic function, or moderate or severe hepatic impairment (classified according to baseline Common Toxicity Criteria grades for AST, alkaline phosphatase and bilirubin) due to liver metastases. It was shown that following daily administration of 250 mg gefitinib, time to steady-state, total plasma clearance ($C_{maxSS)}$ and steady-state exposure (AUC_{24SS}) were similar for the groups with normal and moderately impaired hepatic function. Data from 4 patients with severe hepatic impairment due to liver metastases suggested that steady-state exposures in these patients are also similar to those in patients with normal hepatic function.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to the clinical exposure levels and with possible relevance to clinical use were as follows:
- Corneal epithelia atrophy and corneal translucencies
- Renal papillary necrosis
- Hepatocellular necrosis and eosinophilic sinusoidal macrophage infiltration

Data from non-clinical (*in vitro*) studies indicate that gefitinib has the potential to inhibit the cardiac action potential repolarisation process (e.g. QT interval). Clinical experience has not shown a causal association between QT prolongation and gefitinib.

A reduction in female fertility was observed in the rat at a dose of 20 mg/kg/day. Published studies have shown that genetically modified mice, lacking expression of EGFR, exhibit developmental defects, related to epithelial immaturity in a variety of organs including the skin, gastrointestinal tract and lung. When gefitinib was administered to rats during organogenesis, there were no effects on embryofoetal development at the highest dose (30 mg/kg/day). However, in the rabbit, there were reduced foetal weights at 20 mg/kg/day and above. There were no compound-induced malformations in either species. When administered to the rat throughout gestation and parturition, there was a reduction in pup survival at a dose of 20 mg/kg/day.

Following oral administration of C-14 labelled gefitinib to lactating rats 14 days post-partum, concentrations of radioactivity in milk were 11-19 fold higher than in blood.

Gefitinib showed no genotoxic potential.

A 2-year carcinogenicity study in rats resulted in a small but statistically significant increased incidence of hepatocellular adenomas in both male and female rats and mesenteric lymph node haemangiosarcomas in female rats at the highest dose (10 mg/kg/day) only. The hepatocellular adenomas were also seen in a 2-year carcinogenicity study in mice, which demonstrated a small increased incidence of this finding in male mice at the mid dose, and in both male and female mice at the highest dose. The effects reached statistical significance for the female mice, but not for the males. At no-effect levels in both mice and rats there was no margin in clinical exposure. The clinical relevance of these findings is unknown.

The results of an *in vitro* phototoxicity study demonstrated that gefitinib may have phototoxicity potential.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose (E460)
Croscarmellose sodium
Povidone (K29-32) (E1201)
Sodium laurilsulfate
Magnesium stearate

Tablet coating

Hypromellose (E464)
Macrogol 300
Titanium dioxide (E171)
Yellow iron oxide (E172)

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/Aluminium perforated blister containing 10 tablets or PVC/Aluminium non-perforated blister containing 10 tablets.

Three blisters are combined with an aluminium foil laminate over-wrap in a carton.

Pack size of 30 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

AstraZeneca AB
SE-151 85
Södertälje
Sweden

8. Marketing authorisation number(s)

EU/1/09/526/001
EU/1/09/526/002

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 24th June 2009
Date of latest renewal: 23rd April 2014

10. Date of revision of the text

23rd April 2018

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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APPENDIX 2: SmPC - Methotrexate

18 Methotrexate 25 mg/ml solution for injection

Summary of Product Characteristics Updated 10-Dec-2020 | Accord Healthcare Limited

1. Name of the medicinal product

Methotrexate 25 mg/ml solution for injection

2. Qualitative and quantitative composition

2 ml of solution contains 50 mg methotrexate.
20 ml of solution contains 500 mg methotrexate.
40 ml of solution contains 1000 mg methotrexate.
Excipients with known effect:
4.801 mg/ml (0.208 mmol/ml) sodium.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.
Clear, yellow solution.

4. Clinical particulars

4.1 Therapeutic indications

Acute lymphocytic leukaemia, prophylaxis of meningeal leukaemia, Non-Hodgkin's lymphomas, osteogenic sarcoma, adjuvant and in advance disease of breast cancer, metastatic or recurrent head and neck cancer, choriocarcinoma and similar trophoblastic diseases, advanced cancer of urinary bladder.

4.2 Posology and method of administration

WARNINGS
The **dose must be adjusted carefully** depending on the body surface area if methotrexate is used for the treatment of **tumour diseases.**
Fatal cases of intoxication have been reported after administration of **incorrect calculated** doses. Health care professionals and patients should be fully informed about toxic effects.

Treatment should be initiated by or occur in consultation with a doctor with significant experience in cytostatic treatment.
Methotrexate can be administered intramuscularly, intravenously, intra-arterial or intrathecally. The dosage is generally calculated per m^2 body surface area or body weight. Doses of over 100 mg methotrexate always require subsequent administration of folinic acid (See calcium folinate rescue).
The application and dosage recommendations for the administration of methotrexate for different indications varies considerably. Some common dosages which have been used in different indications are given below. None of these dosages can currently be described as standard therapy. Since the application and dosage recommendations for therapy with methotrexate at high and low dosages vary, only the most commonly used guidelines are given. Current published protocols should be consulted for dosages and the method and sequence of administration.
Methotrexate can be given as convention low dose therapy, intermediate dose therapy, high dose therapy and intrathecal administration.

Conventional low dose therapy: 15-50 mg/m^2 body surface area per week intravenously or intramuscularly in one or more doses. 40-60 mg/m^2 body surface area (for head and neck cancer) once weekly as intravenous bolus injection.
Intermediate dose therapy: Between 100 mg/m^2 to 1000 mg/m^2 body surface area in single dose. In advanced squamous epithelial and bladder cancer, intermediate doses of methotrexate up to 100- 200 mg/m^2 can be used. (See Calcium folinate rescue).
High dose therapy: In several malignant diseases, including malignant lymphoma, acute lymphatic leukaemia, osteogenic sarcoma and metastatic choriocarcinoma, doses of 1000 mg methotrexate or more per m^2 body surface area may be used, administered over a 24-hour period. Administration of folinic acid must begin with 10-15 mg (6-12 mg/m^2) to be given 12-24 hours after starting methotrexate treatment (Further refer to therapy protocols, See calcium folinate rescue).
Calcium folinate rescue
Since the calcium folinate rescue dosage regimen depends heavily on the posology and method of the intermediate or high-dose methotrexate administration, the methotrexate protocol will dictate the dosage regimen of calcium folinate rescue. Therefore, it is best to refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of calcium folinate.
In addition to calcium folinate administration, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the calcium folinate rescue treatment. Renal function should be monitored through daily measurements of serum creatinine.

Adults

Acute lymphocytic leukaemias (ALL)

In low doses, methotrexate is applied within the scope of complex therapy protocols for maintaining remission in adults with acute lymphocytic leukaemias. Normal single doses lie within the range of 20-40 mg/m^2 methotrexate. The maintenance dose for ALL is 15-30 mg/m^2 once or twice weekly.
Other examples:
• 3.3 mg/m^2 in combination with other cytostatic agent once daily for 4-6 week.
• 2.5 mg/kg every week.
• High dose regimen between 1 to 12 g/m^2 (i.v. 1-6 h) repeated every 1-3 weeks.
• 20 mg/m^2 in combination with other cytostatic agents once week.

Breast cancer

Cyclic combination with cyclophosphamide, methotrexate and fluorouracil has been used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. The dose of methotrexate is 40 mg/m^2 intravenously on the first and eighth days of the cycle. The treatment is repeated at 3 week intervals. Methotrexate, in intravenous doses of 10-60 mg/m^2, could be included in cyclic combination regimes with other cytotoxic drugs in the treatment of advanced breast cancer.

Osteosarcoma

Effective adjuvant chemotherapy requires the administration of several cytotoxic chemotherapeutic drugs. In addition to high dose methotrexate with calcium folinate rescue, doxorubicin, cisplatin and a combination of bleomycin, cyclophosphamide and dactinomycin (BCD) can be given. Methotrexate is used in high doses (8,000-12,000 mg/m^2) once weekly. If dose is insufficient to reach real serum concentration of 10^{-3} mol/L at the end of infusion, dose can be increased to 15 g/m^2 for subsequent treatment. Calcium folinate rescue is

necessary. Methotrexate has also been used as the sole treatment in metastatic cases of osteosarcoma.

Older people

Dose reduction should be considered in elderly patient due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Patient with impaired renal function

Methotrexate should be used with caution in patients having impaired renal function. The dose regimens must be adjusted according to the creatinine clearance and serum methotrexate concentrations

- If creatinine clearance (ml/min) is >50, 100% MTX dose can be given
- If creatinine clearance (ml/min) is 20-50, 50% of MTX dose can be given
- If creatinine clearance (ml/min) is <20, MTX should not be given

Patients with impaired hepatic function:

Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially when caused by alcohol. Methotrexate is contraindicated if bilirubin values are >5 mg/dl (85.5 µmol/L).

Paediatric population

Methotrexate should be used with caution in paediatric patients. Treatment should follow currently published therapy protocols for children (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sever liver impairment (See Section 4.2).

Alcohol abuse.

Severe renal impairment (Creatinine clearance less than 20 ml/min, see section 4.2).

Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia.

Serious, acute or chronic infections such as tuberculosis and HIV.

Ulcers of the oral cavity and known active gastrointestinal ulcer disease.

Breast-feeding (see section 4.6).

Concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Fatal toxicity in association with intravenous and intrathecal administration due to dose miscalculation has been reported. Particular caution should be exercised when calculating the dose (see 4.2. posology and administration).

Because of the risk of severe toxic reactions (which can be fatal), methotrexate must only be used in life-threatening neoplastic diseases. Deaths have been reported during treatment of malignancies with methotrexate. The doctor should inform the patient of the risks of treatment and the patient should be monitored constantly by the doctor.

Fertility

Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans during and for a short period after the discontinuation of treatment, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.

Teratogenicity - Reproductive risk

Methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of

childbearing age (see section 4.6). In non-oncologic indications, the absence of pregnancy must be confirmed before Methotrexate 25 mg/ml is used. If women of a sexually mature age are treated, effective contraception must be used during treatment and for at least six months after.
For contraception advice for men see section 4.6.

Tumor lysis syndrome

Like other cytotoxic agents, methotrexate can induce tumour lysis syndrome in patients with rapidly growing tumours. Appropriate supportive treatment and pharmacological measures can prevent or alleviate such complications.

Methotrexate and NSAIDs

Unexpected severe (including fatal) myelosuppression, aplastic anaemia and gastrointestinal toxicity have been reported in connection with concomitant treatment with methotrexate (usually at a high dose) and non-steroidal anti-inflammatory agents (NSAIDs) (see 4.5 interaction with other medicinal products and other forms of interaction).
Concomitant methotrexate treatment and radiotherapy can increase the risk of soft tissue necrosis and osteonecrosis.
Intrathecal and intravenous administration of methotrexate can result in acute encephalitis and acute encephalopathy, possibly with a fatal outcome. Patients with periventricular CNS lymphoma who are given methotrexate intrathecally have reportedly developed cerebral herniation.

Methotrexate and pleural effusion/ascites

Methotrexate is eliminated slowly from collections of fluid (e.g. pleural effusion, ascites). This results in a prolonged terminal half-life and unexpected toxicity. In patients with significant collections of fluid, drainage of the fluid before treatment is started and monitoring of plasma methotrexate levels are recommended.
If stomatitis, diarrhoea, haematemesis or black stool occurs, therapy with methotrexate should be discontinued due to the danger of haemorrhagic enteritis or death from intestinal perforation or dehydration (see section 4.8 undesirable side effects).
Conditions in which there is folic acid deficiency can increase the risk of methotrexate toxicity.
In association with intrathecal administration or in high dose treatment, methotrexate must not be mixed with solutions which contain preservatives (see also 6.6).
Solutions of methotrexate which contain the preservative benzyl alcohol are not recommended for use in infants. Gasping syndrome with fatal outcome has been reported in infants following intravenous treatment with solutions containing the preservative benzyl alcohol. Symptoms include rapid onset of respiratory problems, hypotension, bradycardia and cardiovascular collapse.

Infection or immunological conditions

Methotrexate must be used with great care in connection with active infection and is usually contraindicated in patients with manifest suppression of the immune response or where immunodeficiency is demonstrated by laboratory tests.
Pneumonia (which in certain cases can lead to respiratory failure) can occur.
Potentially fatal opportunistic infections including *Pneumocystis carinii* pneumonia can occur in association with methotrexate treatment. When a patient exhibits pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered (see section 4.8).

Immunisation

Methotrexate may interfere with results of immunological tests Immunisation after a vaccination may be less effective in association with methotrexate treatment. Particularly caution should be exercised in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) due to possible activation. Immunisation with live viruses is not normally recommended.
Skin toxicity*:* Due to the risk of phototoxicity, the patient must avoid sunlight and solarium.

Monitoring treatment

Patients on methotrexate treatment must be closely monitored so that toxic effects can be detected immediately. Analyses before treatment must include a full blood count with differential and platelet counts, liver enzymes, testing for hepatitis B and C infections, renal function test and x-ray of the lungs. Toxic effects of methotrexate can occur even with low doses and therefore it is important to monitor treated patients carefully. Most undesirable effects are reversible if detected early.
After initiation of treatment or when there is a change in the dose, or during periods in which there is an increased risk of elevated levels of methotrexate (e.g. in dehydration), monitoring should be performed.
Bone marrow biopsy must be performed as necessary.
Serum methotrexate level monitoring can significantly reduce methotrexate toxicity and routine monitoring of serum methotrexate level is necessary depending on dosage or therapy protocol.
Leucopenia and thrombocytopenia occur usually 4 -14 days after administration of methotrexate. In rare cases recurrence of leucopenia may occur 12 - 21 days after administration of methotrexate. Methotrexate therapy should only be continued if the benefit outweighs the risk of severe myelosuppression (see section 4.2).
Haematopoietic suppression: Haematopoietic suppression induced by methotrexate may occur abruptly and at apparently safe doses. In the event of any significant drop in leukocytes or platelets, treatment must be discontinued immediately and appropriate supportive therapy instituted. Patients must be instructed to report all signs and symptoms suggestive of infection. In patients concomitantly taking haematotoxic medications (e.g. leflunomide), the blood count and platelets should be closely monitored.
Liver function tests: Particular attention should be paid to the onset of liver toxicity. Treatment should not be initiated or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. Such abnormalities should return to normal within two weeks; after which, treatment may be resumed at the discretion of the doctor. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. This assessment should differentiate between patients without any risk factors and patients with risk factors, e.g. excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.
Screening for liver-related enzymes in serum: A transient rise in transaminase levels to twice or three times the upper limit of normal has been reported with a frequency of 13 - 20%. In the event of a constant increase in liver related

enzymes, consideration should be given to reducing the dose or discontinuing therapy.

Insulin-dependent diabetes

Patients suffering from insulin-dependent diabetes should be carefully monitored because liver cirrhosis and an increase in transaminase can occur.

Due to the potentially toxic effect on the liver, additional hepatotoxic medications should not be given during treatment with methotrexate *unless clearly necessary* and alcohol consumption should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medications (e.g. leflunomide). The same should also be taken into consideration if haematotoxic medications are co-administered.

Malignant lymphomas may occur in patients receiving low-dose methotrexate; in which case, methotrexate must be discontinued. If lymphomas should fail to regress spontaneously, initiation of cytotoxic therapy is required.

Renal function: methotrexate treatment in patients with impaired renal function should be monitored via renal function tests and urinalysis, since impaired renal function reduces the elimination of methotrexate, which may result in severe adverse reactions.

In cases of possible renal impairment (e.g. in elderly patients), close monitoring of renal function is required. This is particularly applies to the co-administration of medicinal products which affect methotrexate excretion cause kidney damage (e.g. non-steroidal anti-inflammatory drugs) or which can potentially lead to haematopoietic disorder. Dehydration may also potentiate the toxicity of methotrexate. Alkalinisation of the urine and increase a high diuresis is recommended.

Respiratory System: Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation (including chest x-ray) should be made to exclude infection. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

Pulmonary symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Pneumonitis can occur at all doses.

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

Children

Methotrexate should be used with caution in paediatric patients. Treatment should follow currently published therapy protocols for children. Serious neurotoxicity, frequently manifested as generalised or focal seizures has been reported with unexpectedly increased frequency among paediatric patients with

acute lymphoblastic leukaemia who were treated with intermediate-dose intravenous methotrexate (1 g/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Elderly

Because of deterioration in liver and kidney function as well as reduced folic acid reserves, relatively low doses should be considered in elderly patients. These patients must be closely monitored for early signs of toxicity.

Sodium

Methotrexate injection contains 345.59 mg (15.033 mmol) of sodium per maximum daily dose (1800 mg). This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Ciprofloxacin

Excretion of methotrexate possibly reduced (increased risk of toxicity).

Non-steroidal anti-inflammatory drugs (NSAIDs).

NSAID preparations must not be given prior to or concomitantly with the high doses of methotrexate used in the treatment of conditions such as osteosarcoma. Concomitant administration of NSAIDs and methotrexate at high doses has reportedly elevated and prolonged serum methotrexate levels, resulting in deaths from severe haematological and gastrointestinal toxicity. NSAID preparations and salicylates have reportedly reduced the tubular secretion of methotrexate in animal models and may increase its toxicity by increasing methotrexate levels. Concomitant treatment with NSAIDs and low doses of methotrexate must therefore be administered with caution.

Nitrous oxide

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression and stomatitis and in case of intrathecal administration increased severe, unpredictable neurotoxicity. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

Leflunomide

Methotrexate in combination with leflunomide can increase the risk of pancytopenia.

Probenecid

Renal tubular transport is diminished by probenecid, and its use together with methotrexate must be avoided.

Penicillins

Penicillins can reduce renal clearance of methotrexate. Haematological and gastrointestinal toxicity have been observed in combination with high and low dose methotrexate.

Oral antibiotics

Oral antibiotics such as tetracycline, chloramphenicol and non-absorbable broad-spectrum antibiotics may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and hence the metabolism of methotrexate by bacteria. In isolated cases, trimethoprim/sulfamethoxazole has reportedly increased myelosuppression in patients treated with methotrexate, probably due to reduced tubular secretion and/or an additive antifolate effect.

Chemotherapeutic products

An increase in renal toxicity can be observed when high doses of methotrexate are given in combination with potentially nephrotoxic chemotherapeutic agents (e.g. cisplatin).

Radiotherapy

Concurrent methotrexate and radiotherapy can increase the risk of soft tissue necrosis and osteonecrosis.

Cytarabine

Concomitant therapy with cytarabine and methotrexate can increase the risk of severe neurological side effects ranging from headache to paralysis, coma and stroke-like episodes.

Hepatotoxic products

The risk of increased hepatotoxicity when methotrexate is administered concurrently with other heptatotoxic products has not been studied. Hepatotoxicity has however been reported in such cases. Patients receiving concomitant treatment with drugs with a known hepatotoxic effect (e.g. leflunomide, azathioprine, sulfasalazine, retinoids) must be carefully monitored for signs of any increase in hepatotoxicity.

Theophylline

Methotrexate can reduce clearance of theophylline. Theophylline levels must therefore be monitored during concomitant treatment with methotrexate.

Mercaptopurine

Methotrexate increases plasma content of mercaptopurine. The combination of methotrexate and mercaptopurine can therefore require dose adjustment.

Drugs with high plasma protein binding

Methotrexate is partially bound to serum albumin. Other highly bound drugs such as salicylates, phenylbutazone, phenytoin and sulfonamides can increase the toxicity of methotrexate by means of displacement.

Furosemide

Concomitant administration of furosemide and methotrexate can result in increased levels of methotrexate due to competitive inhibition of tubular secretion.

Vitamins

Vitamin preparations containing folic acid or its derivatives can cause a reduced response to systemically administered methotrexate, however conditions in which there is a deficiency of folic acid can increase the risk of methotrexate toxicity.

Proton pump inhibitors

Literature data indicate that co-administration of proton pump inhibitors and methotrexate, especially at high dose, may result in elevated and prolonged plasma levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicity.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males

It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.
As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.
Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications. If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development. In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related). Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.
• Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
• Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in in disease-matched patients treated with drugs other than methotrexate.
Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected, in particular at doses commonly used in oncologic indications
When methotrexate was discontinued prior to conception, normal pregnancies have been reported.
When used in oncological indications, methotrexate should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If the drug is used during pregnancy or if the patient becomes pregnant while taking methotrexate, the patient should be informed of the potential risk to the foetus.
Breastfeeding
Methotrexate passes into breast milk in quantities such that there is a risk to the child even at therapeutic doses. Breast feeding must therefore be discontinued during treatment with methotrexate.
Fertility

Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases. In oncologic indications, women who are planning to become pregnant are advised to consult a genetic counselling centre, if possible, prior to therapy and men should seek advice about the possibility of sperm preservation before starting therapy as methotrexate can be genotoxic at higher doses (see section 4.4).

4.7 Effects on ability to drive and use machines

Since fatigue and dizziness can occur as an undesirable effect, ability to react and judgement can be impaired, which should be taken into account for example when driving or carrying out work involving a high degree of precision.

4.8 Undesirable effects

Conventional and high dose therapy

The frequency and degree of severity of undesirable effects depends on the dose administered, the duration of exposure and method of administration, but side effects have been seen at all doses and can occur at any time during treatment. Most undesirable effects are reversible when detected at an early stage. When severe reactions occur, the dose should be reduced or treatment discontinued and appropriate measures initiated (see 4.9). If treatment with methotrexate is resumed, this should be done with caution after adequate consideration of the further need for the drug. Increased vigilance with regard to any recurrence of toxicity is required.

The most frequently reported undesirable effects include ulcerative stomatitis, leukopenia, nausea and bloating. Other frequently reported undesirable effects are feeling unwell, unusual tiredness, chills and fever, dizziness, reduced resistance to infections. Treatment with folinic acid during high dose therapy can counteract or alleviate a number of undesirable effects. Temporary discontinuation of therapy is recommended if there are signs of leukopenia.

Organ system class	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)	**Not known** (cannot be estimated from the available data)
Infections and infestations		Herpes zoster			Sepsis, opportunistic infections (may be fatal in some cases), infections caused by the cytomegaly virus	
Cardiac disorders				Pericarditis pericardial		

				effusion pericardial tamponade		
Blood and lymphatic system disorders		leukocytopenia, thrombocytopenia and anaemia	Pancytopenia agranulocytosis haematopoietic disorders	Megaloblastic anaemia	Severe courses of bone marrow depression aplastic anaemia Lymphadenopathy , eosinophilia and neutropenia, Lympho-proliferative disorders	Haemorrhage, haematoma
Immune system disorders			Anaphylactoid reactions, allergic vasculitis		Immunosuppression hypogamma-globulinaemia	
Psychiatric disorders					Insomnia, cognitive dysfunction	psychosis
Nervous system disorders		Headache fatigue drowsiness	Vertigo confusion depression seizures convulsion encephalopathy	Severely impaired vision mood alterations paresis, effect on speech including dysarthria and aphasia, myelopathy	Pain, muscular asthenia or paresthesia of the extremities, myasthenia, changes in sense of taste (metallic taste), meningism (paralysis, vomiting), acute aseptic meningitis	
Eye disorders				visual disturbances, blurred vision	Conjunctivitis Retinopathy, transient blindness/loss of vision,	

					periorbital oedema, blepharitis, epiphora, photophobia	
Neoplasms benign malignant and unspecified (incl cysts and polyps)			individual cases of lymphoma which abated in a number of cases once methotrexate treatment had been discontinued.		Tumour lysis syndrome	
Vascular disorders			Vasculitis	hypotension thromboembolic events reactions (incl. arterial thrombosis, cerebral thrombosis, thrombophlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism)		Cerebral oedema, petechie
Respiratory, thoracic and mediastinal disorders		Pulmonary complications due to interstitial alveolitis/pneumonitis and related deaths (independent of dose and duration of methotrexate treatment).	Pulmonary fibrosis	Pharyngitis, apnoea, bronchial asthma	Pneumocystis carinii pneumonia, shortness of breath, chronic obstructive pulmonary disease. Infections including pneumonia have also	Acute pulmonary oedema

		Typical symptoms may be: general illness; dry, irritating cough; shortness of breath progressing to rest dyspnoea, chest pain, fever. If such complications are suspected, methotrexate treatment must be discontinued immediately and infections (including pneumonia) must be excluded.			been observed. Pleural effusion	
Gastrointestinal disorders	Loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth	Diarrhoea (especially during the first 24-48 hours after administration of methotrexate).	gastrointestinal bleeding and ulcers, pancreatitis	Gingivitis, Enteritis, melaena (bloody stools), malabsorption	Haematemesis (vomiting blood), toxic megacolon	Toxic megacolon

	and throat (especially during the first 24-48 hours after administration of methotrexate). Stomatitis, dyspepsia					
Hepato-biliary disorders	Increase in liver-related enzymes (ALAT, ASAT, alkaline phosphatase and bilirubin).		Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); diabetic complications; drop of serum albumin.	Acute hepatitis and hepatotoxicity	Reactivation of chronic hepatitis, acute liver degeneration. Furthermore, herpes simplex hepatitis and liver insufficiency have been observed (also see the notes regarding liver biopsy in section 4.4).	Metabolic disorder
Skin and subcutaneous tissue disorders		Exanthema, erythema, itching	Urticaria, photosensibility, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaque;	Increased pigmentary changes of nails, acne, petechiae, ecchymoses, erythema multiforme, cutaneous	Furunculosis, teleangiectasis, acute paronychia, Furthermore, nocardiosis, histoplasma and cryptococcus mycosis and disseminated	Skin exfoliation / dermatitis exfoliative, skin necrosis,

			severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).	erythematous eruptions.	herpes simplex have been reported. Allergic vasculitis, hidradenitis	
Musculoskeletal system, connective tissue and bone disorders			Osteoporosis, Arthralgia, myalgia	Stress fracture		Osteonecrosis of jaw (secondary to lympho-proliferative disorders)
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	Renal failure, oliguria, anuria, azotaemia, hyperuricaemia elevated serum creatinine and urea level	Proteinuria	
Reproductive system and breast disorders			Inflammation and ulceration of the vagina		Loss of libido, impotence,oligospermia, impaired menstruation, Vaginal discharge, infertility, gynaecomastia	
General disorders and administration site			Severe allergic reactions progressing to anaphylactic shock;		Fever, impaired wound healing	

conditions						
Metabolism and nutrition disorders				Diabetes Mellitus		

The following undesirable effects have also been reported, but their frequency has not been established: Pneumocystis carinii pneumonia, (including reversible cases), foetal death, damage to the foetus, abortion.

Systemic organ toxicity

Lymphoma

Malignant lymphoma which can go into remission after discontinuation of the treatment with methotrexate can occur in patients on low dose therapy, and may not therefore require any cytotoxic treatment. Methotrexate should be discontinued first and appropriate treatment initiated if the lymphoma does not regress.

Haematological

Methotrexate can suppress haematopoiesis and cause anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia. Methotrexate must be administered with caution to patients with malignancies and underlying factors affecting haematopoiesis. When treating neoplastic conditions, treatment with methotrexate should only be given provided the potential benefits outweigh the risk of myelosuppression.

Lungs

Lung disease caused by methotrexate, including acute or chronic interstitial pneumonitis, is a potentially dangerous complication, which can occur at any time during the course of treatment. This undesirable effect has been reported at low doses and is not always totally reversible. Deaths have been reported. Signs of pulmonary involvement or symptoms such as dry non-productive cough, fever, chest pains, dyspnoea, hypoxemia and infiltrate on x-ray of the lungs, or non-specific pneumonitis which occurs in connection with methotrexate therapy, may indicate potentially serious damage and requires discontinuation of treatment and careful investigation. Lung changes can occur at all doses. The possibility of infection (including pneumonia) must be excluded.

Gastrointestinal

If vomiting, diarrhoea or stomatitis occur, with resulting dehydration, methotrexate therapy must be discontinued until the patient has recovered. Haemorrhagic enteritis and deaths caused by intestinal perforation can occur. Methotrexate must be used with great caution in patients with peptic ulcers or ulcerative colitis. Stomatitis can be prevented or alleviated by folinic acid mouthwashes.

Liver

Methotrexate involves a potential risk of acute hepatitis and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal and occurs commonly after long-term use (in general after 2 years or more) and after a total cumulative dose greater than 1.5 g. In studies of psoriasis patients hepatotoxicity was seen to be proportional to the cumulative dose and was potentiated by alcoholism, overweight, diabetes and age.

Transient deterioration in liver enzyme values is frequently seen after methotrexate treatment and does not usually necessitate adjustment of treatment. Existing abnormal liver values and/or reduction in serum albumin can indicate severe hepatotoxicity.

Methotrexate has caused reactivation of hepatitis B infections and exacerbation of hepatitis C infections, in some cases with fatal outcome. Some cases of hepatitis B reactivation have occurred following discontinuation of methotrexate. Clinical and laboratory tests should be performed to investigate any occurrence of liver disease in patients with prior hepatitis B or C infections. Based on these investigations, treatment with methotrexate may prove unsuitable for certain patients.
In the event of impaired liver function, the undesirable effects of methotrexate (in particular stomatitis) can be exacerbated.
Kidneys
Methotrexate can cause kidney damage which can result in acute renal failure. Renal function can be exacerbated following high dose therapy to such an extent that the excretion of methotrexate is inhibited, as a result of which systemic methotrexate toxicity can occur. In order to prevent renal failure, alkalinisation of the urine and adequate fluid intake (at least 3 l/day) are recommended. Measurement of serum methotrexate and renal function is recommended.
Skin
Serious, in some cases fatal skin reactions, including toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome and erythema multiforme have been reported within a few days of oral, intramuscular, intravenous or intrathecal treatment with methotrexate in single or repeat doses. Radiation dermatitis and sunburn can be accentuated after use of methotrexate.
CNS
There are reports of leukoencephalopathy after intravenous treatment with methotrexate in patients who have undergone craniospinal radiotherapy. Severe neurotoxicity, often manifested as generalised or focal seizures have been reported with an unexpected increase in frequency in children with acute lymphoblastic leukaemia treated with a moderately high dose of intravenous methotrexate (1 g/m2). Symptomatic patients frequently had leukoencephalopathy and/or microangiopathic calcifications in x-ray investigations.
Chronic leukoencephalopathy has also been reported in patients treated with repeated high doses of methotrexate together with folinic acid, even without concomitant cranial radiotherapy. Discontinuation of the methotrexate therapy did not always result in full recovery. Leukoencephalopathy has also been reported in patients treated with methotrexate tablets.
One transient acute neurological syndrome has been observed in patients undergoing high dose therapy. Manifestations of this neurological syndrome can include abnormal behaviour, focal sensorimotor symptoms including transient blindness, and abnormal reflexes. The exact cause is unclear.
Cases of neurological side effects ranging from headache to paralysis, coma and stroke-like episodes have been reported, primarily in children and adolescents receiving concomitant medication with cytarabine.
Intrathecal therapy
The subacute neurotoxicity is usually reversible after discontinuing methotrexate.

Organ system class	**Common (>1/100)**
Central and peripheral nervous system disorders	Headache, chemical arachnoiditis, subacute neurotoxicity, necrotising demyelinating leukoencephalopathy

Gastrointestinal disorders	Nausea and vomiting
General disorders and administration site conditions	Fever

Chemical arachnoiditis, which can occur a few hours after intrathecal administration of methotrexate is characterised by headache, back pain, stiff neck, vomiting, fever, meningism and pleocytosis in the cerebrospinal fluid similar to that in bacterial meningitis. Arachnoiditis generally disappears within a few days.
Subacute neurotoxicity, common after frequently repeated intrathecal administration, mainly affects the motor functions in the brain or spinal cord. Paraparesis/paraplegia, with involvement of one or more spinal nerve roots, tetraplegia, cerebellar dysfunction, cranial nerve paralysis and epileptic seizures can occur.
Necrotising demyelinating leukoencephalopathy can occur several months or years after starting intrathecal therapy. The condition is characterised by progressive neurological deterioration with insidious onset, confusion, irritability and somnolence. Ultimately severe dementia, dysarthria, ataxia, spasticity, seizures and coma can occur. The condition can be fatal. Leukoencephalopathy occurs primarily in patients who have received large quantities of intrathecal methotrexate in combination with cranial radiotherapy and/or systemically administered methotrexate.
Signs of neurotoxicity (meningeal inflammation, transient or permanent paresis, encephalopathy) must be followed up after intrathecal administration of methotrexate.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
The Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Experience of overdose with the product has in general been associated with oral and intrathecal treatment, although overdose in association with intravenous and intramuscular administration has also been reported.
Reports of oral overdose have often been due to accidental daily instead of weekly ingestion. Commonly reported symptoms following oral overdose include the symptoms and signs seen at pharmacological doses, in particular haematological and gastrointestinal reactions such as leukopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, myelosuppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In certain cases no symptoms were reported. There are reports of deaths associated with overdose. In these cases there were also reports of conditions involving sepsis or septic shock, renal failure and aplastic anaemia.
The most common symptoms of intrathecal overdose are CNS symptoms including headache, nausea and vomiting, seizures or convulsions and acute toxic encephalopathy. In certain cases, no symptoms were reported. There have

been reports of deaths following intrathecal overdose. In these cases there were also reports of cerebellar herniation accompanying elevated intracranial pressure and toxic encephalopathy.

Recommended treatment

Antidote therapy: Folinic acid should be given parenterally at a dose at least the size of the methotrexate dose and should wherever possible be administered within an hour. Folinic acid is indicated to minimise toxicity and counter the effect of methotrexate overdose. Folinic acid treatment should be initiated as soon as possible. The longer the interval between the administration of methotrexate and the initiation of folinic acid, the less the effect of folinic acid in suppressing the toxic effect. Monitoring of serum methotrexate concentrations is necessary to be able to determine the optimum dose of folinic acid and the length of the treatment. In the event of a major overdose, hydration and alkalinisation of the urine may be required to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither standard haemodialysis nor peritoneal dialysis have been shown to increase the elimination of methotrexate. Acute intermittent haemodialysis with the use of highly permeable dialyser may be attempted for methotrexate intoxication.

Intrathecal overdose may require intensive systemic supportive measures such as systemic administration of high doses of folinic acid, alkaline diuresis, acute CSF drainage and ventricular lumbar perfusion.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytostatic agent: folic acid analogue

ATC code: L01BA01

Methotrexate is a folic acid antagonist with a cytostatic effect. Methotrexate inhibits the conversion of folic acid to tetrahydrofolic acid since the compound has a greater affinity for the enzyme dihydrofolate reductase than the natural substrate folic acid. As a result, DNA synthesis and new cell formation are inhibited. Methotrexate is s-phase specific. Actively proliferating tissues such as malignant cells, bone marrow, foetal cells, epithelium and buccal and intestinal mucosa are generally most susceptible to methotrexate.

5.2 Pharmacokinetic properties

Following intravenous administration, peak serum concentrations of methotrexate are reached after approx. 0.5 – 1 hour. There is wide inter-individual and intra-individual variation, especially with repeated doses. Saturation of oral absorption occurs at doses above 30 mg/m^2. About half of the absorbed methotrexate is bound to plasma proteins, but binding is reversible, and methotrexate is easily diffused into the cells, with the highest concentrations reached in the liver, spleen and kidneys in the form of polyglutamate can be found which can be retained for few weeks or months. Methotrexate also passes to a lesser degree into cerebrospinal fluid. The half-life is approx. 3 to 10 hours with low dose therapy and approx. 8 to 15 hours with high dose therapy. Elimination from plasma is triphasic and the majority of the methotrexate is excreted unchanged in urine within 24 hours.

5.3 Preclinical safety data

Animal studies show that methotrexate impairs fertility and that it is embryotoxic, foetotoxic and teratogenic. Methotrexate is mutagenic in vivo and in vitro, but the clinical significance is unknown since rodent carcinogenicity studies have produced differing results. Chronic toxicity studies in mice, rats and dogs showed

toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride
Sodium hydroxide (For pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Owing to the absence of compatibility studies, this medicine should not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials - 2 years
Vial after first opening – Use immediately after opening.
After dilution – 24 hours
Chemical and physical stability of the diluted solution have been demonstrated for 24 hours. For microbial point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and condition prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 25°C.
For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

For 2 ml: Clear glass vial (USP type 1), sealed with a grey butyl rubber stopper and orange flip-off cap.
For 20 ml and 40 ml: Clear glass vial (USP type 1), sealed with a grey butyl rubber stopper and lavender flip-off cap.

Package size: 1 vial in carton for 2 ml, 20 ml and 40 ml pack size
10 vials per packs for 20 ml and 40 ml

Not all the pack size may be marketed .

6.6 Special precautions for disposal and other handling

The solution should be visually inspected prior to use. Only clear solution practically free from particles should be used.
Methotrexate injection may be further diluted with an appropriate preservative-free medium such as glucose solution (5%) or sodium chloride solution (0.9%).
With respect to the handling the following general recommendations should be considered: The product should be used and administered only by trained personnel; the mixing of the solution should take place in designated areas, designed to protect personnel and the environment (e.g safety cabins); protective clothing should be worn (including gloves, eye protection, and masks if necessary).
Pregnant healthcare personnel should not handle and/or administer Metotrexate.
Methotrexate should not come into contact with the skin or mucosa. In the event of contamination, the affected area must be irrigated immediately with copious quantities of water at least ten minutes.
For single use only. Any unused solution should be discarded. Waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (as the patient's body fluids and excreta may also contain appreciable amounts of antineoplastic agents and it has been suggested that they, and material such as bed linen contaminated with them, should also be treated as

hazardous waste). Any unused product or waste should be disposed of in accordance with local requirements by incineration.
Adequate procedures should be in place for accidental contamination due to spillage; staff exposure to antineoplastic agents should be recorded and monitored.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

PL 20075/0344

9. Date of first authorisation/renewal of the authorisation

03/07/2012

10. Date of revision of the text

03/12/2020

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12/2020
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APPENDIX 3:

20 Flowchart