DEPARTMENT OF HEALTH
Republic of South Africa

SAHPRA
South African Health Products Regulatory Authority

MEDICINES AND HUMAN REPRODUCTION

This guidance document is intended to provide guidance to applicants regarding the safety assessment and labelling of medicines with regard to human reproduction health. It represents the current thinking of the South African Health Products Regulatory Authority (SAHPRA) on the assessment and labelling of medicines with regard to safety in human reproduction. SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications. Guidelines and application forms are available from the office of the Chief Executive Officer and the website.

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1 PURPOSE OF THIS GUIDANCE DOCUMENT

1.1 To inform industry on the regulatory requirements regarding the information to be submitted to the Authority, with an application for registration of a medicine, and what information is to be included in a concise format, where relevant, in the human reproduction section of the professional information of the medicine, and the patient information leaflet. Professional information of the medicine (Regulation 11 and Professional Information Guideline), should also appear in the patient information leaflet, where relevant, in lay language. (Regulation 12 and Patient Information Leaflet Guideline)

1.2 To inform industry regarding the assignment of risk categories for medicine use in pregnancy and lactation (breastfeeding/breast milk) and give examples of statements to be considered, where relevant, for inclusion in the human reproduction section of the professional information of the medicine.

1.3 To give guidance to authorised prescribers regarding the prescribing of medicines that may interfere with human reproduction, pregnancy/labour/delivery and lactation (breastfeeding/breast milk) and the newborn baby.

1.4 This guidance document is only applicable to medicines which have significant systemic absorption/exposure after administration by the approved route of administration, for the approved indication(s), at the approved dose/dosage regimen and for the approved duration of treatment.

1.5 The guidance document does not address an idiosyncratic reaction to a medicine which crosses the placenta, an over dosage of a medicine, an accidental exposure to a medicine, addiction to a medicine or other substances with health hazards.

1.6 A decision as to whether text in the “Human Reproduction” section of the professional information of the medicine, should be in bold print and/or underlined and/or boxed and/or copied/moved to another section in the professional information of the medicine, will be at the discretion of the Authority.

1.7 Reference in this guidance document to the word “medicine” includes the active ingredient(s), the metabolite(s) of the active ingredient(s), excipients and diluent, where relevant, as any of the ingredients or all of them as well as the metabolites, may be harmful to human reproduction, pregnancy, lactation (breastfeeding) and the newborn.

2 INTRODUCTION

2.1 General information

2.1.1 The active ingredient(s), the metabolite(s), excipients and/or diluent, where relevant, of a medicine can cause harm to the conceptus/embryo and developing foetus at any time during pregnancy, from conception up to labour and delivery. Harm is not limited to medicine use in the first trimester of pregnancy.

2.1.2 The severity of harm will depend on the type of medicine or medicines used, the medicine dose, route of administration, the frequency and duration of exposure, and the timing of exposure during pregnancy.

2.1.3 The possibility of harm to the conceptus and developing foetus are increased when the mother is also suffering from, and treated for, certain diseases/conditions/disorders (e.g. epilepsy), if she is exposed to radiation (e.g. high dose X rays), if she contracts certain infections during pregnancy (e.g. Rubella) or is involved in certain lifestyle related activities known to be harmful for the conceptus/developing foetus (e.g. frequent alcohol use and tobacco smoking).

2.1.4 Harm may include an early abortion, death of the developing foetus, major foetal structural abnormalities, especially with exposure in the first trimester, which is the period of primary morphogenesis. Exposure after the first trimester may cause abnormalities in organ development, differentiation, metabolism and growth with various degrees of functional abnormalities/functional impairment of the organs and homeostatic mechanisms involved.

2.1.5 The labour/delivery process may be affected, which may compromise the condition of the baby during and after the birth process.

2.1.6 Further harm to the newborn baby may occur if the baby is breastfeeding or receives mothers own expressed breast milk or other babies who receive the mother`s donated breast milk to a breast milk bank, which contains the medicine and/or its metabolites, which may cause harm to other babies receiving the donated breast milk.

2.1.7 The effects of harm/insults to the conceptus and developing foetus during pregnancy are usually irreversible, and may have a significant impact on the heath and quality of life of the newborn baby, extending into infancy, childhood, adolescence and adulthood. The parents are burdened with an abnormal baby/child who may have a detrimental impact on their marriage/relationship/family life, with significant financial implications for treatment and educational/schooling needs.

2.1.8 The fact that a medicine is marketed and used by patients for many years without published reports of harm to human reproduction or pregnancy outcomes, does not necessarily imply that the medicine is safe, or exclude a potential risk of harm, due to a lack of reliable/robust data on the effect of the medicine on human reproduction and pregnancy outcomes.

2.1.9 Men and women of child bearing age, who are on treatment with a medicine which may harm the reproduction system of both men and women as well as do harm during pregnancy, should not donate blood/blood components for (indicate how many) days/weeks/months after completion of treatment, men should not plan to father a child, should use barrier contraception, and not donate sperm or semen for (indicate how many) days/ weeks/months after completion of treatment. Females should not become pregnant, should use highly effective contraception, and should not donate ova, whilst on treatment with the medicine until (indicate how many) weeks/months after completion of treatment.

2.2 Vaccine use in pregnancy

2.2.1 Vaccines containing replicating agents (e.g. live attenuated viral/bacterial vaccines) are contraindicated in pregnancy. The proposed statements, where relevant, to be considered for inclusion in the Human Reproduction section of the professional information of the vaccine/medicine, will be in accordance with the Pregnancy Safety Risk Category requirements for the specific vaccine/medicine which should also include a statement that the vaccine should not be administered to women planning to become pregnant within (indicate how many) weeks/months before a planned pregnancy.

2.2.2 The following vaccines are safe to use in pregnancy to protect the mother and/or newborn infant: tetanus toxoid (adsorbed), inactivated influenza vaccine, acellular pertussis vaccine and combination vaccines such as TDaP (Tetanus / Diphtheria / acellular Pertussis) and TDaP/IPV (Tetanus / Diphtheria / acellular Pertussis / Inactivated Polio vaccine). The proposed statements, where relevant, to be considered for inclusion in the Human Reproduction section of the professional information of the vaccine/medicine, will be in accordance with the Pregnancy Risk Category for the specific vaccine/medicine.

2.3 Biological medicines (category A biological medicines)

2.3.1 In general the same precautionary measures and Pregnancy Safety Risk Categories as for use of non-biological category A medicines, will be applicable, where relevant, to category A biological medicines until proven otherwise by robust published evidence on safety, when used in the various trimesters of pregnancy or a particular trimester in pregnancy as well as during lactation, demonstrating no detectable harm to the mother, the conceptus/embryo or developing foetus and the newborn.

2.3.2 The proposed statements, to consider, where relevant, for inclusion in the Human Reproduction section of the professional information of the biological medicine, will be in accordance with the Safety Risk Category requirements for the specific biological medicine, where applicable to men and women of child bearing age, in terms of contraception, planning to father a child, planning to become pregnant, pregnancy, breastfeeding, donating sperm or semen, donating ova, donating breast milk to breast milk banks and donating blood and/or blood components, whilst on treatment with these medicines.

2.4 Complementary medicines (category D medicines)

2.4.1 In general the same precautionary measures and Pregnancy Safety Risk Categories as for use of category A biological and category A non-biological medicines, will be applicable, where relevant, to these medicines until proven otherwise by robust published evidence on safety, when used in the various trimesters of pregnancy or a particular trimester in pregnancy as well as during lactation, demonstrating no detectable harm to the mother, the conceptus/embryo or developing foetus and the newborn.

2.4.2 The proposed statements to consider, where relevant, for inclusion in the Human Reproduction section of the professional information of the medicine, will be in accordance with the Pregnancy Safety Risk Category requirements for the specific complementary medicine where applicable to men and women of childbearing age, in terms of contraception, planning to father a child, becoming pregnant, pregnancy, breast feeding, donating sperm or semen, donating ova, donating breast milk to breast milk banks and donating blood and/or blood components, whilst on treatment with the medicine.

2.5 Inhalation (general) anaesthetics / intravenous sedative medicines used in anaesthesia

2.5.1 In general the same precautionary measures and Pregnancy Safety Risk Categories as for category A biological and category A non-biological medicines will be applicable, where relevant, for use of inhalation (general) anaesthetics/intravenous sedative medicines used in anaesthesia, in women of child bearing age and during pregnancy until proven otherwise by published robust evidence on safety when used in pregnancy demonstrating no detectable harm to the mother, the conceptus, embryo or developing foetus and the newborn.

2.5.2 The potential risk of harm during pregnancy of a single, relatively short exposure to any inhalation (general) anaesthetic/intravenous sedative medicine used in anaesthesia, in a controlled environment, is low.

However repeated and/or prolonged exposure to any inhalation (general) anaesthetic and/or any intravenous sedative used in anaesthesia, during all trimesters of pregnancy or a particular trimester of pregnancy, may increase the risk of harm to the developing foetus. The proposed statements to be included, where relevant, in the Human Reproduction section of the professional information of the medicine used in anaesthesia, will be in accordance with the requirements of the Pregnancy Safety Risk Category where applicable to pregnancy and lactation for that medicine.

2.6 Radiopharmaceuticals

2.6.1 Radiopharmaceuticals are medicines/compounds which are radioactive and are used for diagnostic and/or therapeutic purposes.

2.6.2 These medicines/compounds are contra-indicated for use in pregnancy and lactation until proven otherwise by robust published evidence on safety when used in the various trimesters of pregnancy or a particular trimester of pregnancy as well as during lactation/breastfeeding, demonstrating no detectable harm to the mother, conceptus/embryo, the developing foetus and the newborn. The proposed statements to be considered for inclusion, where relevant, in the Human Reproduction section of the professional information of the medicine, will be in accordance with the requirements of the Pregnancy Safety Risk Category of the specific radiopharmaceutical medicine, where applicable to pregnancy and breast feeding

2.6.3 In addition, international and national guidelines on the safe use of radiopharmaceuticals in men, women of child bearing age, pregnancy and lactation (breast feeding), should be consulted before using these medicines/compounds.

2.7 African Traditional Medicines

2.7.1 In general the same precautionary measures and Pregnancy Safety Risk Categories as for biological category A medicines and non-biological category A medicines will be applicable, where relevant, to African Traditional Medicines, until proven otherwise by robust published evidence of safety when used in the various trimesters of pregnancy or a particular trimester of pregnancy as well as during lactation, demonstrating no detectable harm to the mother, conceptus/embryo developing foetus or newborn. The proposed statements to be considered for inclusion, where relevant, in the Human Reproduction section of the professional information of the medicine, will be in accordance with the requirements of the Pregnancy Safety Risk Category of the specific medicine, where applicable to pregnancy and breastfeeding.

2.8 Clinical Trials

2.8.1 Pregnant women or women planning to become pregnant, are usually excluded from human clinical trials where new chemical molecules or medicines with no information on safety in pregnancy/lactation are investigated for the treatment of a particular disease/condition or disorder.

2.8.2 When males and females of child bearing age are to be enrolled in clinical studies where medicines, known to be harmful, or potentially harmful to human reproduction organs and pregnancy are to be used, the appropriate international and national guidelines regulating such research, should be consulted.

3 INFORMATION TO BE CONSIDERED FOR INCLUSION, WHERE RELEVANT, IN THE HUMAN REPRODUCTION SECTION OF THE PROFESSIONAL INFORMATION OF THE MEDICINE

3.1 General information

It should be stated in the Human Reproduction section of the professional information of the medicine, whether the medicine, its metabolites, excipients and/or diluent, where relevant, interfere or may interfere with human/animal sexual behaviour / human reproduction organs and the control / regulation thereof as listed in paragraphs 3.3.1 to 3.3.5 (inclusive) of this document, which may directly or indirectly have an impact on human/animal reproduction.

In the event that a medicine, its active ingredient(s), metabolite(s), excipient(s) or diluent, where relevant, has or may have an impact on any of the items listed in paragraphs 3.3.1 to 3.3.5 (inclusive) of this document, a concise and relevant description of each of the following items should be supplied:

3.1.1 The effect(s) and the significance/implications of the effect(s) on the various aspects of human / animal sexual behaviour or human / animal reproduction or human / animal reproduction organs and the regulation/control thereof, as listed, should be described.

3.1.2 The duration and magnitude of the effect(s).

3.1.3 The reversibility/irreversibility (complete/partial) of the effect(s) and time to complete reversibility (back to pre-treatment status).

3.1.4 The risk minimisation measures / action(s) to be considered or to be taken in view of the effect(s) on male fertility/procreation ability, female fertility/ability to conceive, pregnancy, labour/delivery, newborn baby and lactation (breastfeeding/breast milk), to minimise the anticipated effect(s) and/or risks.

3.2 Examples of statements to be considered

Examples of statements to be considered where relevant, for inclusion in the human reproduction section of the professional information of the medicine, as part of risk minimisation measures/activities:

3.2.1 The use of contraceptives, type of contraceptive (barrier and/or hormonal), use before initiating treatment, during treatment and after treatment. Indicate the time to start contraception before initiating treatment and for how long to continue with contraception after completion of treatment, before it is safe for women of child bearing age, to become pregnant and men to father a child. (If a woman uses a hormonal contraceptive, the interaction and the effect(s) thereof, if any, with the medicine to be used by her for treatment, should be stated).

Indicate whether male contraception is needed as the medicine or its metabolites may cross to the female partner via semen. Men being treated with this medicine are advised not to father a child during treatment for (indicate for how many) days/weeks/months following the last dose of treatment.

3.2.2 Conservation of sperms/ova for later use. This should be considered before starting treatment with the medicine. This statement is important where the medicine may damage one or more aspects of the male and or female reproduction capability, especially with uncertainty regarding reversibility to normal fertility/pre-treatment fertility status or where permanent damage to one or more of the male/female reproduction organ systems, is expected.

3.2.3 Mothers should not breastfeed their babies or administer mothers own expressed breast milk to their babies, when on treatment with the medicine. The medicine or its metabolite(s) crosses in breast milk and may harm the newborn baby or causes adverse events. The harm/possible adverse events should be described/listed, if known

The medicine and/or its metabolites appear(s) in the milk of female animals but no information is available for humans, therefore women on treatment with the medicine should not breastfeed their babies as the possibility of harm due to exposure of the newborn to the medicine or its metabolites in breast milk, cannot be excluded. Mothers on treatment with this medicine, should not donate their breast milk to breast milk banks for (indicate for how many) weeks/months after completion of treatment as the medicine and/or its metabolites appear in breast milk.

3.2.4 A medically/laboratory supervised pregnancy test (urine/blood) should be performed (indicate how many) days before initiating treatment to exclude pregnancy and at frequent intervals during treatment and for (indicate for how many) weeks/months after completion of treatment, to ensure that pregnancy has not occurred.

3.2.5.1 This medicine is contraindicated for use in pregnancy and in mothers breastfeeding their infants or administering expressed mothers own breast milk to them.

Give a concise description of the damage/harm that the medicine has caused to the animal/human conceptus/embryo/developing foetus in the different trimesters or a particular trimester of pregnancy and the animal baby/ human newborn and the harm/damage to the animal/human baby that could result from breastfeeding or feeding the animal baby/ human baby their mothers own expressed breast milk.

3.2.5.2 Mothers on treatment should not donate their breast milk to breast milk banks for (indicate for how many) days/weeks/months after completion of treatment.

3.2.5.3 Women should be counselled and educational materials made available to them, to ensure they understand why they should not become pregnant when on treatment with the medicine.

3.2.5.4 Advice on contraception during treatment should be given. A medically/laboratory supervised pregnancy test (urine/blood) should be done before initiating treatment to exclude pregnancy and medically/laboratory supervised pregnancy tests (urine/blood) should be performed with frequent intervals during treatment until (indicate for how many) days/weeks/months after completion of treatment.

3.2.5.5 If a woman becomes pregnant whilst on treatment, further counselling and/or termination of the pregnancy (a therapeutic abortion) should be considered. (Consult relevant South African Law(s) regarding termination of pregnancy/abortion/guidelines on termination of pregnancy.)

If termination of pregnancy (TOP) is not an option, and treatment is unavoidable and cannot be delayed until after the birth of the baby, or a safe or safer alternative medicine is not available, cannot be tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and written consent be obtained, preferable from both partners (if available/traceable), to continue with treatment.

3.2.5.6 If information on any aspect of human/animal sexual behaviour/human reproduction organs, and the hormonal regulation / control thereof, if relevant, as listed in paragraphs 3.3.1 to 3.3.5 (inclusive) of this document, is not available, it should be stated

3.2.5.7 Mothers/men on treatment with this medicine, should not donate blood/blood components, whilst on treatment and for (indicate for how many) days/weeks/months after discontinuing treatment with this medicine, to prevent harm to the reproductive organs of men/women and harm to the conceptus/embryo/developing foetus during pregnancy.

3.2.5.8 Men should not donate semen, and women should not donate ova whilst on treatment with this medicine and for (indicate for how many) days/weeks/months after completion of the treatment.

3.2.5.9 Other measures e.g. pregnant mothers, or women of child bearing age, planning to become pregnant, should not handle/prepare medicines which are known to be teratogenic or harmful to the conceptus/embryo or developing foetus, for patients in health care facilities/ home care or own family members at home. If this is unavoidable, they should use appropriate protection to prevent or minimise the risk of being exposed to the medicine e.g. use appropriate protective eye gear, hand washing, gloves, face masks and make use of a laminar flow cabinet.

3.3 Effect(s) of the medicine on human/animal reproduction

3.3.1 Effect(s) of the medicine on human/animal *male* reproduction to be considered, where relevant, for inclusion in the human reproduction section of the professional information of the medicine

3.3.1.1 Sexual behaviour
- (i) Change in libido/sexual interest
- (ii) Change in sexual behaviour

3.3.1.2 Sexual intercourse
- (i) Erectile dysfunction including impotence
- (ii) Inability to achieve an orgasm, ejaculation disorders

3.3.1.3 Ejaculate
- (i) Changes in ejaculate volume
- (ii) Concentration of the medicine or its metabolites, present in the ejaculate (semen, seminal fluid)
- (iii) Sperm count, sperm morphology, sperm motility, harm to sperm genetic material

3.3.1.4 Genital organs
- (i) Testis atrophy, testis volume, change in testis function (spermatogenesis)
- (ii) Seminal vesicles/vas deferens dysfunction
- (iii) Changes in prostate gland function, including hormonal function, secretions and susceptibility to infections

3.3.1.5 Changes to hypothalamic-pituitary-testicular axis hormones/regulation thereof

3.3.1.6 Fertility
- (i) Impaired fertility (reversible/irreversible)
- (ii) Infertility (reversible/irreversible)

3.3.2 Effect(s) of the medicine on human/animal *female* reproduction to be considered, where relevant, for inclusion in the human reproduction section of the professional information of the medicine

3.3.2.1 Sexual behaviour
- (i) Change in libido/sexual interest
- (ii) Change in sexual behaviour

3.3.2.2 Sexual intercourse
- (i) Failure to get an orgasm/dyspareunia

3.3.2.3 Menstrual cycle
- (i) Irregular menstrual cycles/ unpredictability of a menstrual cycle/ amenorrhoea
- (ii) Changes in the duration of a cycle/menstrual bleeding pattern/volume
- (iii) Irregular ovulation
- (iv) Dysmenorrhoea
- (v) More intense bleeding/sparse bleeding/break through bleeding (excluding menstruation)

3.3.2.4 Changes in the premenstrual dysphoric syndrome

3.3.2.5 Genital organs

(i) Suppression or stimulation of ovary function/ovulation

(ii) Changes in fallopian tube motility and function

(iii) Changes in uterus tone or uterine endometrial lining, making it unfavourable to implantation of a fertilised ovum, uterine endometrial bleeding

(iv) Changes to cervical tone and specialised mucus secretion e.g. increase in viscosity of mucus

3.3.2.6 Changes to the hypothalamic-pituitary-ovarian axis hormone secretion and control

3.3.2.7 Fertility

(i) Impaired fertility (reversible/irreversible)

(ii) Infertility (reversible/irreversible)

3.3.2.8 Changes in the ability to conceive

3.3.3 Effect(s) of medicine on human/animal pregnancy/outcome of pregnancy to be considered for inclusion, where relevant, in the human reproduction section of the professional information of the medicine

3.3.3.1 The effect(s) of the medicine on uterus function and its ability to retain the conceptus e.g. implantation of fertilised ovum

3.3.3.2 The medicine or its metabolites crosses the placenta to the foetus and/or damages the placenta and/or reduces the placental perfusion and/or function(s)

3.3.3.3 Evidence of harm to the conceptus/ embryo and/or developing foetus, organ growth, differentiation and function with exposure in the first trimester, second trimester or third trimester

3.3.3.4 Effects on intra uterine growth parameters of foetus (weight, length, head circumference)

3.3.3.5 Change in the risk of an abortion

3.3.3.6 Change in the risk of a foetal death/intrauterine death

3.3.3.7 Change in the risk of an ectopic pregnancy

3.3.3.8 Change in the duration of pregnancy e.g. leading to premature births or post mature births

3.3.3.9 Change in the labour/delivery process e.g. prolongation of labour

3.3.4 Effect(s) of the medicine on the human/animal newborn baby, infant, child and in later life, to be considered for inclusion, where relevant, in the human reproduction section of the professional information of the medicine

3.3.4.1 Perinatal

(i) Changes impacting on the condition of the baby after birth including the need for monitoring, resuscitation and the development of conditions/disorders necessitating treatment

(ii) Changes detrimental to the adaptation of the baby to the extra uterine environment

(iii) Measurements (length, birthweight, head circumference, organ size)

(iv) Change in the risk of perinatal mortality/ morbidity, including the possibility of structural abnormalities, growth and/or changes in the function of the various organ/body systems, including the metabolic and homeostatic mechanisms

(v) Congenital structural, growth and/or functional/metabolic abnormalities, extending to infancy, childhood and adulthood

3.3.4.2 Postnatal

(i) An increased risk/susceptibility to develop certain neonatal conditions, disorders or diseases in postnatal period, including feeding difficulties

(ii) The risk of withdrawal syndrome (give description), if relevant

3.3.4.3 Infancy, childhood and adolescence

(i) Changes in weight, length, head circumference, growth rate and neurodevelopmental (milestone) development

(ii) Emergence of unexpected neurodevelopmental/neuropsychiatric/behavioural disorders

(iii) Other abnormalities/disorders noticed in infancy, childhood and adolescence e.g. school performance

3.3.5 Effect(s) of the medicine on human/animal lactation (breastfeeding)/breast milk to be considered for inclusion, where relevant, in the human reproduction section of the professional information of the medicine

3.3.5.1 Indicate whether the medicine and/or its metabolites crosses into breast milk. Give the concentration of the medicine/metabolites in breast milk, if available.

3.3.5.2 List/describe the anticipated effect(s) on the baby due to the excretion of the medicine and/or its metabolites into breast milk.

3.3.5.3 Indicate whether there is any interference with the hormonal control of breast milk production resulting in either suppression / inhibiting of breast milk production or stimulation of breast milk production.

3.3.5.4 Indicate whether the medicine or its metabolites changes the nutritional value/composition, volume or taste of breast milk.

3.3.5.5 Indicate whether it is safe for the mother to breastfeed her baby/administer her own expressed breast milk to her baby and whether it is safe to donate breast milk to a breast milk bank.

3.3.5.6 See also the information in paragraph 3.2.3 of this document.

4 ASSIGNMENT OF SAFETY RISK CATEGORIES FOR USE OF A MEDICINE IN PREGNANCY AND LACTATION / BREASTFEEDING

4.1 The assignment of a safety risk category for use of a medicine in pregnancy and lactation, is based on the collective weight, robustness and consistency of the evidence emanating from the following data sources

4.1.1 Pharmacology/pharmacodynamics/pharmacokinetic properties and toxicology of the medicine and/or class of medicines

4.1.2 Laboratory study data/non clinical *in vitro/in vivo* data

4.1.3 Animal study data (preclinical animal data). Reproduction toxicity and developmental toxicity studies

4.1.4 Human clinical study data and/or human post- marketing exposure data to the medicine e.g. pregnancy exposure registries, birth-defect registries, case studies, spontaneous reports of exposure to the medicine in pregnancy, epidemiological studies, periodic safety update reports/periodic benefit risk evaluation reports (PSURs/PBRERs)

4.2 Evidence taken into consideration from each of the data sources used, to determine the safety risk category for use of the medicine in pregnancy and lactation

4.2.1 Pharmacology/pharmacodynamics/pharmacokinetic properties and toxicology of the medicine/class of medicines

4.2.1.1 Evidence indicative of teratogenicity, genotoxicity, mutagenicity, embryo toxicity, foetal harm, foetal death or other harm to the developing foetus in the various trimesters or a particular trimester of pregnancy, including the effect(s) on labour and the delivery process.

4.2.1.2 Evidence indicative of harm to the placenta, its perfusion and/or function

4.2.1.3 Evidence indicative of maternal toxicity

4.2.1.4 Evidence indicative of interference with the process of labour and/or delivery

4.2.1.4 Evidence indicative of interference of the medicine in the hormonal control/regulation or other aspects of breast milk production, and the excretion of the medicine and/or its metabolites in breast milk.

4.2.2 *In vitro/in vivo* data/laboratory data

Evidence indicative of genotoxicity, mutagenicity, cytotoxicity or other harm to the conceptus/embryo/developing foetus during the various trimesters or a particular trimester of pregnancy.

4.2.3 Animal data on reproduction toxicity and developmental toxicity

Evidence from animal studies (name the different species used) demonstrating harm to aspects of animal reproduction ability/fertility, sexual cycle, maternal toxicity, pregnancy and the duration thereof, teratogenicity, embryo or foetal toxicity, abortions, congenital/structural abnormalities, growth and functional/metabolic abnormalities of organ/body systems, deaths or other abnormalities/dysfunctions during the various time periods of pregnancy.

Evidence of interference / harm relating to the labour/delivery process, the condition of newborn animals at birth and juvenile animals until sexual maturity.

The relevance of the evidence in animals to human reproduction, pregnancy and lactation, should be assessed as well as the relevance of the doses used in animals to the human equivalent doses recommended for similar indications and whether in animals, a dose response relationship and consistency in terms of harm caused by the medicine, during pregnancy, labour and delivery, were demonstrated

Evidence that the medicine and/or its metabolites is excreted in animal mother's milk and the effect(s) thereof on the baby animal.

4.2.3.1 Reproduction toxicity

Evidence of interference / harm to reproduction in the parental generation (Fo generation). Any effects on male or female sexual behaviour, harm of structure, or function of the reproduction organs or related endocrine systems, including gamete production and transport, reproduction cycle, fertility, conception, gestation, parturition, pregnancy outcomes, lactation, or modification of other functions that are dependent on the integrity of the reproduction system.

4.2.3.2 Developmental toxicity

(i) Evidence of developmental toxicity in the animal progeny (F1 generation) including effects which manifested in the embryonic or foetal period due to exposure of the conceptus, embryo and developing foetus to the medicine during pregnancy and lactation or effects which manifested after birth or later.

(ii) Developmental toxicity includes evidence indicative of teratogenicity, embryo/foetal toxicity, abortions, deaths, congenital abnormalities in structure, growth, differentiation or function or other abnormalities/conditions of the newborn/offspring at birth and with follow up until at least sexual maturity of the juvenile animal.

4.2.3.3 The following should be considered in the assessment of the relevance of extrapolating evidence emanating from animal data to human reproduction, pregnancy, labour, delivery and lactation/breastfeeding

(i) The choice of animal species/more than one animal species used to conduct studies

(ii) The pharmacology / pharmacodynamics / pharmacokinetic properties and toxicity of the molecule/medicine or class of medicines

(iii) The route of administration of the medicine

(iv) The dose of the medicine and duration of exposure to the medicine and during which time period of pregnancy

(v) The effects of toxicity on the conceptus/embryo/developing foetus due to exposure during pregnancy and lactation/breastfeeding

(vi) The mechanism(s) of toxicity

(vii) Whether there is evidence indicative of a dose response relationship regarding harm to the conceptus/ embryo/developing foetus

(viii) Whether there is evidence of cross animal species consistency regarding reproduction toxicity and/or developmental toxicity effects

(ix) The harmful effects of a medicine or its metabolite(s) on animal reproduction organs (structure/function/control) including pregnancy, labour, delivery, the developing foetus, the newborn and lactation/breastfeeding, are not necessarily predictive of the effects of the medicine on human reproduction organs (structure/function/control), pregnancy, labour, delivery, the human foetus, the newborn and lactation/breastfeeding; however the animal findings should create an awareness of a risk / potential risk of harm to humans.

4.2.4 Human data on exposure to the medicine in pregnancy and lactation

4.2.4.1 Evidence of harm due to exposure to the medicine during the various trimesters of pregnancy, or a particular trimester of pregnancy, obtained from clinical study data and/or post-marketing sources such as post-marketing use of the medicine, epidemiological studies, case control studies, spontaneous reports of exposure, unintended/accidental exposure to the medicine during pregnancy, pregnancy exposure registries, birth defect registries and periodic safety update reports (PSURs) and periodic benefit risk evaluation reports (PBRERs).

4.2.4.2 Evidence on human reproduction indicative of a risk of reversible / irreversible impairment / harm of male or female fertility and the duration thereof if reversible, or other aspects of human reproduction, including hormonal control/regulation thereof, and sexual behaviour.

4.2.4.3 Evidence indicative of harm/toxicity to the conceptus, embryo or developing foetus with exposure during the various trimesters or a particular trimester, of pregnancy and the effects on the newborn, infant and child until adolescence.

The type of harm/toxicity and the severity thereof, should be considered.

If there seems to be an association between exposure of the medicine and harm to the conceptus/embryo/developing foetus, the association should be considered in terms of strength, consistency, specificity, dose response relationship and whether the association with the type of harm does correlate with the timing of the exposure of the conceptus/embryo/developing foetus to the stage of development of the conceptus/embryo/foetus.

4.2.4.4 Evidence of an association of harm due to exposure to the medicine, should be compared to/viewed against, the background rate of similar harm detected in medicine unexposed pregnancies, to decide whether there is indeed an increased risk of harm with exposure to the medicine.

4.2.4.5 Evidence that the medicine and/or its metabolite(s), interferes with the hormonal control of lactation/breastfeeding, volume of breast milk produced, nutritional composition thereof, the taste of breast milk as well as whether the medicine and/or its metabolites is excreted into breast milk and the anticipated effects on the newborn.

5 PREGNANCY SAFETY RISK CATEGORIES

5.1 Safety Risk Category: Unknown Risk/ Indeterminate Risk

5.1.1 No or insufficient robust/reliable information/evidence relating to the various aspects of human reproduction, including pregnancy and lactation/breastfeeding, is available/obtainable, based on

- the pharmacology/pharmacodynamics/pharmacokinetic properties and toxicology of the medicine/class of medicines,
- *in vitro/in vivo* data/laboratory data,
- animal reproduction toxicity and development toxicity data
- human clinical data, including post marketing use of the medicine, spontaneous reports of exposure to the medicine in pregnancy, unintended/accidental exposure to the medicine in pregnancy, epidemiological studies, case studies, pregnancy exposure registries, birth defect registries, PSURs/PBRERs, to assign a risk category with any certainty, and make a recommendation for use of the medicine in pregnancy and lactation.

5.1.2 Proposed statements to be considered, where relevant, for inclusion in the human reproduction section of the professional information of the medicine:

SAFETY RISK CATEGORY: UNKNOWN / INDETERMINATE RISK

5.1.2.1 It is unknown / indeterminate whether and how the medicine may interfere with human reproduction and whether the medicine is safe to use in any, or a particular trimester of pregnancy.
It is unknown / indeterminate whether breastfeeding a baby would be safe as it is unknown whether the medicine and/or its metabolites is/are excreted in breast milk.

5.1.2.2 The medicine may be considered for use in pregnancy and lactation / breastfeeding if an alternative medicine, which is known to be safe or safer for use, is not available, has failed, cannot be tolerated or is contraindicated and treatment is unavoidable and cannot be delayed until after the birth of the baby. Both partners (if available/traceable) should be counselled and written consent, preferably from both partners (if available/traceable), should be obtained before initiating treatment with the medicine. (Include statements, where relevant, contained under paragraph 5.1.2.5 below.)

5.1.2.3 Women should not become pregnant when treatment is considered / planned and should not be treated with the medicine during any or a particular trimester of pregnancy.
A medically / laboratory supervised pregnancy test (urine/blood) should be performed (indicate how many) days before initiating treatment to exclude pregnancy.

The medically / laboratory supervised pregnancy testing (urine/blood), issuing the prescription and dispensing the medicine should occur on the same day. Further medically / laboratory supervised pregnancy tests (urine/blood) should be considered during treatment to exclude pregnancy.
Highly effective contraception should be initiated in women (indicate how many) days/weeks before starting treatment, and be continued during treatment until (indicate how many) days/weeks after completion of the treatment;

5.1.2.4 The male partner should use barrier contraception if he is on treatment with the medicine, and his non pregnant female partner, should use highly effective contraception to prevent pregnancy, until (indicate how many) days/weeks after her male partner completed his treatment with the medicine. Males should not donate sperm or semen during treatment until (indicate how many) days/weeks/months after treatment has been completed;

5.1.2.5 If a woman is already pregnant before initiating treatment, and treatment is unavoidable, and cannot be delayed until after the birth of the baby, and no safe or safer alternative medicine is available, cannot be tolerated, is contraindicated or has failed**, the following additional statements should be considered for inclusion:**

- It is unknown / indeterminate whether the medicine can cause structural / developmental / functional / metabolic harm, and/or abortion / death of the embryo / developing foetus, when used in any trimester or a particular trimester of pregnancy;
- Both partners (if available/traceable) should be counselled and written consent, preferably from both partners (if available/traceable), should be obtained before initiating treatment with the medicine;
- Conservation of sperm/ova should be considered for later use before initiating treatment;
- The medicine should not be used in the first trimester of pregnancy if possible;
- Use the lowest effective dose of the medicine for treatment and for the shortest recommended treatment period;
- Mother and embryo/foetal wellbeing should be frequently monitored by appropriate methods, e.g. serum markers, ultrasound, amniocentesis and by clinical methods
- Discontinue the medicine if there is evidence of harm to the mother and/or embryo/developing foetus;

  The possibility of termination of the pregnancy (TOP) (therapeutic abortion) should be considered and discussed, preferably with both partners (if available/traceable), if there is evidence of severe harm and/or abnormalities to the embryo/developing foetus. (Consult relevant South African Law(s)/guidelines on termination of pregnancy/abortion.)
  If termination of pregnancy (TOP) is not an option, and treatment is unavoidable, and cannot be delayed until after the birth of the baby, and no safe or safer alternative medicine is available, cannot be tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and written consent be obtained, preferably from both partners (if available/traceable), to continue with treatment;
- Mothers should only breastfeed their babies or administer their own expressed breast milk to them, if formula feeding is not available / affordable or not considered as a feeding option to them. Mothers should not donate breast milk to breast milk banks. It is unknown whether the medicine or its metabolite(s) is excreted in breast milk. However, the possibility of harm to the newborn baby, due to exposure to the medicine and/or its metabolite(s), if excreted in breast milk, cannot be excluded;

- If the male partner is on treatment with the medicine, he should use barrier contraception and his non-pregnant female partner highly effective contraception. If his female partner is already pregnant, she should use a barrier contraceptive method. Male and female contraception should continue until (indicate how many) days/weeks/months after the treatment of the male partner has been completed.

5.2 Safety Risk Category: Insignificant Risk

Evidence from the following data sources, did not demonstrate any detectable safety risk with the use of the medicine in any trimester or a particular trimester of pregnancy, and the medicine and/or its metabolites are either not excreted in breast milk, or excreted in undetectable quantities. There is also no detectable evidence that the medicine interferes with any aspect of human reproduction based on all of the following listed data sources:

- Human clinical data, including post marketing use of the medicine, case studies, epidemiological studies, spontaneous reports of exposure to the medicine in pregnancy, unintended/accidental exposure to the medicine in pregnancy, pregnancy exposure registries, birth defect registries, periodic safety update reports (PSURs)/periodic benefit risk evaluation reports (PBRERs)
- Animal reproduction toxicity and development toxicity data, on the use of the medicine during pregnancy and lactation
- *In vitro/in vivo* data/laboratory data
- The pharmacology/pharmacodynamics/pharmacokinetic properties and toxicology of the medicine/class of medicines

5.2.1 Proposed statements to consider, where relevant, for inclusion in the human reproduction section of the professional information of the medicine:

SAFETY RISK CATEGORY: INSIGNIFICANT RISK

5.2.2.1 The medicine can be used in pregnancy and lactation/breastfeeding. There is no detectable evidence of embryo/foetal harm with the use of the medicine during any trimester or a particular trimester of pregnancy and mothers can breastfeed their babies, or administer their own expressed breast milk to their babies or donate breast milk to a breast milk bank, whilst on treatment with the medicine;

5.2.2.2 Men on treatment with the medicine can donate sperm/semen and females on treatment with the medicine can donate ova.

5.3 Safety Risk Category: Possible Risk

- The relevant pharmacology/pharmacodynamics/pharmacokinetic properties and toxicology of the medicine/class of medicines indicate a possible risk of harm to the conceptus/embryo/developing foetus, if used during any or a particular trimester of pregnancy, and/or to the breastfeeding newborn.
- However there is no, limited, or inconclusive evidence of harm, to the conceptus/embryo/developing foetus or the breastfeeding newborn, based on available *in vitro/in vivo* data/laboratory data, animal reproduction toxicity and development toxicity data, as well as human clinical study data including post marketing use of the medicine, case studies, spontaneous reports of exposure to the medicine during pregnancy, unintended/accidental exposure to the medicine in pregnancy, epidemiological studies, pregnancy exposure registries, birth defect registries and PSURs/PBRERs.

5.3.1 Proposed statements to be considered, where relevant, for inclusion in the human reproduction section of the professional information of the medicine:

SAFETY RISK CATEGORY: POSSIBLE RISK

5.3.1.1 The possibility of structural/developmental/functional/metabolic harm, and or abortion/death of the conceptus/embryo/developing foetus cannot be excluded with certainty when using the medicine in any or a particular trimester of pregnancy.

5.3.1.2 The medicine may be considered for use in pregnancy and lactation/breastfeeding if an alternative medicine, which is known to be safe or safer for use, is not available, cannot be tolerated, is contraindicated, has failed and treatment is unavoidable and cannot be delayed until after the birth of the baby.

5.3.1.3 Women of child bearing age should not plan a pregnancy or become pregnant when treatment is considered/planned and a medically/laboratory supervised pregnancy test (urine/blood) should be done (indicate how many) days before initiating treatment to exclude pregnancy and frequently repeated during pregnancy to exclude whether pregnancy has occurred during treatment.
Highly effective contraception in the non-pregnant female partner should be initiated (indicate how many) days/weeks/months before initiating treatment and continued until (indicate how many) days/weeks/months after completion of treatment.
Male partners of females on treatment with the medicine should use barrier contraception until (indicate how many) days/weeks/months after the treatment of their female partner has been completed.

5.3.1.4 If a woman is already pregnant and treatment is unavoidable and cannot be delayed until after the birth of the baby, with no safe or safer alternative medicine available, not tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and written consent, preferably from both partners (if available/traceable), be obtained before initiating treatment with the medicine.

The following additional statements should, where relevant, be considered for inclusion:

- The medicine should not be used in the first trimester of pregnancy if possible
- Use the lowest effective dose of the medicine for treatment and for the shortest recommended treatment period
- Mother and embryo/foetal wellbeing should be frequently monitored by appropriate methods during pregnancy e.g. clinical methods, serum markers, ultrasound, and amniocentesis
- Discontinue the medicine if there is any evidence of possible harm to the mother or conceptus/embryo/developing foetus
- The possibility of termination of the pregnancy (therapeutic abortion) should be considered and discussed with both partners (if available / traceable) if there is evidence of severe harm and/or abnormalities to the embryo/foetus. (Consult relevant South African Law(s) regarding termination of pregnancy/guidelines on termination of pregnancy/abortion.)
  If termination of pregnancy is not an option, and treatment is unavoidable and cannot be delayed until the birth of the baby and no safe or safer alternative medicine is available, cannot be tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and written consent be obtained, preferably from both partners (if available/traceable) to continue with treatment.

- Mothers should only breastfeed their babies or administer their own expressed breast milk to them, if formula feeding is not available/affordable or not considered as a feeding option to them. The possibility of harm to the baby, due to exposure to the medicine and/or its metabolites excreted in breast milk, cannot be excluded.
  Mothers should not donate breast milk to a breast milk bank whilst on treatment with the medicine.

5.3.1.5 Women of child bearing age and not pregnant, should not donate ova whilst on treatment with the medicine until (indicate how many) days/weeks/months after completion of treatment.

5.3.1.6 Men on treatment with the medicine should use a barrier contraceptive and their female partners a highly effective contraceptive method, if not pregnant or a barrier contraceptive method, if already pregnant, until (indicate how many) days/weeks/months after completion of male partners treatment.

5.3.1.7 Men on treatment with the medicine should not donate sperm or semen until (indicate how many) days/ weeks/months after completion of treatment.

5.4 Safety Risk Category: Probable Risk

- Both the relevant pharmacology/pharmacodynamics/pharmacokinetic properties and toxicology of the medicine/class of medicines and *in vitro/in vivo* data/laboratory data indicate a probability of harm to the conceptus/embryo/developing foetus, if used during any trimester or a particular trimester of pregnancy, or to the newborn through exposure to the medicine and/or its metabolites in breast milk.
- However there is no, limited, or inconclusive evidence of harm to the conceptus/embryo/developing foetus or breastfeeding newborn, based on the animal reproduction toxicity and development toxicity data and human clinical study data, including post marketing use of the medicine, spontaneous reports of exposure to the medicine in pregnancy, unintended/accidental exposure to the medicine in pregnancy, epidemiological studies, case reports, pregnancy exposure registries, birth defect registries, or PSURs/PBRERs.

5.4.1 Proposed statements to be considered, where relevant, for inclusion in the human reproduction section of the professional information of the medicine:

SAFETY RISK CATEGORY: PROBABLE RISK

5.4.1.1 The probability of structural/developmental/functional/metabolic harm, and/or abortion/death of the conceptus/ embryo/developing foetus cannot be excluded when using the medicine in any or a particular trimester of pregnancy

5.4.1.2 The medicine may be considered for use in pregnancy and lactation/breastfeeding if an alternative medicine, which is known to be safe or safer for use in any trimester of pregnancy and during lactation/breastfeeding, is not available, cannot be tolerated, has failed, is contraindicated and treatment is unavoidable and cannot be delayed until after the birth of the baby

5.4.1.3 Women should not become pregnant when treatment is considered or planned.
Women should start using highly effective contraception and their male partners barrier contraception (indicate how many) days/weeks before treatment is initiated and until (indicate how many) days/weeks/months after completion of treatment with the medicine.
A medically/laboratory supervised pregnancy test (urine/blood) should be performed before initiating treatment to exclude pregnancy and at frequent intervals during treatment to exclude whether pregnancy has occurred and until (indicate how many) days/weeks/months after completion of treatment.

5.4.1.4 If the woman is already pregnant and treatment is unavoidable and cannot be delayed until after the birth of the baby and no safe or safer alternative medicine is available, or cannot be tolerated, has failed, or is contraindicated, both partners (if available/traceable) should be counselled and written consent, preferably from both partners (if available/traceable), be obtained before initiating treatment with the medicine.

The following additional statements, where relevant, should be considered for inclusion:

- The medicine should not be used in the first trimester of pregnancy if possible.
- Use the lowest effective dose of the medicine for treatment and for the shortest recommended time period.
- Mother and embryo/foetal wellbeing should be frequently monitored by appropriate methods, e.g. serum markers, ultrasound, amniocentesis and by clinical methods.
- Discontinue the medicine if there is any evidence of probable harm to the mother or embryo/developing foetus.
- The possibility of termination of the pregnancy (therapeutic abortion) should be considered and discussed with both partners (if available/traceable), if there is evidence of severe harm and/or abnormalities to the embryo/developing foetus. (Consult relevant South African Law(s)/guidelines on termination of pregnancy/abortion.)
  If termination of pregnancy is not an option and treatment is unavoidable, and cannot be delayed until after the birth of the baby or no safe or safer alternative medicine is available, cannot be tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and written consent be obtained, preferably from both partners (if available/traceable), to continue with treatment
- Mothers should only breastfeed their babies or administer their own expressed breast milk to them, if formula feeding is not available/affordable or not considered as a feeding option to them. The probability of harm to the baby, due to exposure to the medicine and/or its metabolites excreted in breast milk, cannot be excluded. Mothers should not donate their breast milk to a breast milk bank whilst on treatment until (indicate how many) days/weeks/months after completion of the treatment.

5.4.1.5 Females of child bearing age should not donate ova whilst on treatment with the medicine until (indicate how many) days/weeks/months after completion of treatment.

5.4.1.6 Males on treatment with the medicine should not donate sperm or semen until (indicate how many) days/ weeks/months after completion of treatment.

5.4.1.7 Males on treatment with the medicine should use barrier contraception and their female partners should, if not pregnant, use highly effective contraception or if pregnant, a barrier contraceptive method, until (indicate how many) days/weeks/months after completion of treatment of the male partner.

5.5 Safety Risk Category: Definite Risk

- Data on the relevant pharmacology/pharmacodynamics/pharmacokinetic properties and toxicology of the medicine/class of medicines, *in vitro / in vivo* data / laboratory data as well as animal reproduction toxicity and development toxicity data, implicate a definite risk of harm/death for the conceptus/embryo/developing foetus, if used during any trimester or a particular trimester of pregnancy, and / or to the breastfeeding newborn baby.

- However there is no, limited, or inconclusive human clinical study data, including data on post-marketing use of the medicine, epidemiological studies, spontaneous reports of exposure to the medicine in pregnancy, unintended / accidental exposure to the medicine in pregnancy, case reports, pregnancy exposure registries, birth defect registries and PSURs/PBRERs, implicating harm/death to the conceptus/embryo/developing foetus or to the breastfeeding newborn baby.

5.5.1 Proposed statements, where relevant, to be considered for inclusion in the human reproduction section of the professional information of the medicine

SAFETY RISK CATEGORY: DEFINITE RISK

5.5.1.1 There is a definite risk of structural, developmental or functional/metabolic harm, and/or abortion/death of the conceptus/embryo/developing foetus, when the medicine is used during any or all trimesters of pregnancy.

5.5.1.2 The medicine should only be considered for use in pregnancy and lactation if treatment is unavoidable or cannot be delayed until after the birth of the baby or an alternative medicine, which is known to be safe or safer for use in pregnancy and lactation, is not available, cannot be tolerated, has failed or is contraindicated.

5.5.1.3 Women should not become pregnant when treatment is considered or planned. A medically/laboratory supervised pregnancy test (urine/blood) should be done (indicate how many) days before initiating treatment, to exclude pregnancy and further medically/laboratory supervised pregnancy tests (urine/blood) should be considered to exclude pregnancy until (indicate how many) days/weeks/months after completion of treatment.
Highly effective contraception should be used by the non-pregnant female partner and barrier contraception by the male partner, during treatment. Contraception should be started by both the female and male partner (indicate how many) days/weeks/months before initiating treatment and continued until (indicate how many) days/weeks/months after completion of treatment.

5.5.1.4 The medically/laboratory supervised pregnancy testing (urine/blood), issuing the prescription and dispensing the medicine should occur on the same day.

5.5.1.5 If the woman is already pregnant, treatment with the medicine should only be considered if an alternative medicine, which is known to be safe or safer for use in pregnancy, is not available, cannot be tolerated, has failed, is contraindicated, and treatment is unavoidable and cannot be delayed until after the birth of the baby.

5.5.1.6 Both partners (if available/traceable) should be counselled and written consent, preferably from both partners (if available/traceable), be obtained before initiating treatment with the medicine in the pregnant female partner.

In such cases the following additional statements, where relevant, should be considered for inclusion:

- The medicine should not be used in the first trimester of pregnancy if possible.
- Use the lowest effective dose of the medicine for treatment and for the shortest duration recommended.
- Mother and embryo/foetal wellbeing should be frequently monitored by appropriate methods, e. g. serum markers, ultrasound, amniocentesis and clinical methods.
- Treatment with the medicine must be stopped, if there is evidence suggesting definite harm to the mother and/or the embryo/developing foetus.

- The possibility of termination of the pregnancy (therapeutic abortion) should be considered and discussed with both partners (if available/traceable), if there is evidence of severe harm and/or abnormalities to the embryo/foetus. (Consult relevant South African Law(s)/guidelines on termination of pregnancy/ abortion.)
  If termination of pregnancy is not an option and treatment is unavoidable and cannot be delayed until after the birth of the baby, or a safe or safer alternative medicine is not available, cannot be tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and written consent be obtained, preferably from both partners (if available/traceable) to continue with treatment.
- Conservation of sperm/ova for later use should be considered before initiating treatment.
- Mothers should only breastfeed their babies or administer their own expressed breast milk to them, if formula feeding is not available/affordable or not considered as a feeding option to them. Definite harm to the newborn baby, due to exposure to the medicine and/or its metabolites excreted in breast milk, cannot be excluded.
- Mothers should not donate their breast milk to a breast milk bank until (indicate how many) days/weeks/months after completion of the treatment.

5.5.1.7 Women of child bearing age should not donate ova whilst on treatment with the medicine until (indicate how many) days/weeks/months after completion of the treatment.

5.5.1.8 Men on treatment with the medicine should not donate sperm or semen whilst on treatment with medicine until (indicate how many) days/weeks/months after completion of the treatment.

5.5.1.9 Male partners on treatment should use barrier contraception and their female partner, if not pregnant, highly effective contraception, and if pregnant, a barrier type of contraceptive method, until (indicate how many) days/weeks/months after completion of treatment of the male partner.

5.6 Safety Risk Category: Identified Risk (Contraindication)

- Harm was identified/demonstrated in the human conceptus/embryo/developing foetus including death, abortion and harm done to structure, development, growth, differentiation, metabolism or function of organs/organ systems when exposure to the medicine occurred in any trimester of pregnancy or a particular trimester of pregnancy, by human clinical study data, including human post marketing exposure data to the medicine in pregnancy, spontaneous and other case reports, unintended/accidental exposure to the medicine in pregnancy, epidemiological studies, pregnancy exposure registries, birth defect registries and PSURs/PBRERs.
- Any of following findings may or may not be present: Animal reproduction and developmental toxicity data, *in vitro/in vivo* data/laboratory data as well as the relevant pharmacology, pharmacodynamics/pharmacokinetic properties and toxicology of the medicine/class of medicines demonstrated/identified harm when used in any trimester or a particular trimester of pregnancy, which included harm done related to structure, development, growth, differentiation, metabolism or function of organs/organ systems, abortion/death of the conceptus, embryo/developing foetus. Harm was demonstrated or could not be excluded, in newborn babies due to exposure to the medicine and/or its metabolites, excreted in breast milk.

5.6.1 Proposed statements, where relevant, to be considered for inclusion in the human reproduction section of the professional information of the medicine

SAFETY RISK CATEGORY: IDENTIFIED RISK (CONTRAINDICATION)

5.6.1.1 The medicine must not be used in pregnancy and lactation (See contraindications).

5.6.1.2 Identified harm relating to the use of the medicine in any trimester or a particular trimester of pregnancy, has been demonstrated in humans e.g. one or more of the following: genotoxicity, teratogenicity, abortion, foetal death, abnormalities of foetal organ structure, organ development/differentiation/growth, metabolism and function. Abnormalities of organ structure, metabolism and/or function in the newborn and neurodevelopmental / behaviour / neuropsychiatric and other abnormalities / disorders extending to infancy, childhood, adolescence and adulthood, have been demonstrated.

5.6.1.3 Women should not plan a pregnancy or become pregnant when treatment is considered/planned and a medically/laboratory supervised pregnancy test (urine/blood) should be done (indicate how many) days before initiating treatment to exclude pregnancy and frequently repeated during treatment, to exclude whether pregnancy has occurred.

Highly effective contraception in the non-pregnant female partner should be started (indicate how many) days/weeks/months before treatment is initiated and continued for the duration of treatment and until (indicate how many) days/weeks/months after completion of treatment. The male partner should use barrier contraception whilst his non-pregnant female partner is on treatment until (indicate how many) days/weeks/months after completion of her treatment

5.6.1.4 The medically/laboratory supervised pregnancy testing (urine/blood), issuing the prescription and dispensing of the medicine should occur on the same day.

5.6.1.5 Conservation of sperm/ova for later use should be considered before initiating treatment with the medicine if there is a risk of permanent/irreversible damage to the reproduction system of one or both partners.

5.6.1.6 If a woman becomes pregnant whilst on treatment with the medicine, treatment should be discontinued and both partners (if available/traceable) be counselled. The possibility of termination of the pregnancy (therapeutic abortion) should be considered and discussed with both partners (if available/traceable) if there is already evidence of severe harm and/or abnormalities of the embryo/developing foetus. (Consult relevant South African Law(s)/guidelines on termination of pregnancy/abortion).

If termination of pregnancy is not an option, and treatment is unavoidable and cannot be delayed until after birth of the baby, she should be treated with an alternative medicine which is known to be safe or safer for use in pregnancy.

If no safe or safer alternative medicine is available, cannot be tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and written consent, preferably from both partners (if available/traceable), be obtained to continue treatment with the medicine.

5.6.1.7 If a woman is already pregnant before initiating treatment, and treatment is unavoidable and cannot be delayed until after the birth of the baby, she should be treated with an alternative medicine which is known to be safe or safer for use in pregnancy.

If no safe or safer alternative medicine is available, or cannot be tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and the possibility of termination of the pregnancy should be considered and discussed with them. (Consult relevant South African Law(s)/guidelines on termination of pregnancy/abortion).

If termination of pregnancy is not an option, and treatment is unavoidable, and cannot be delayed until after the birth of the baby and no safe or safer alternative medicine is available, cannot be tolerated, has failed or is contraindicated, both partners (if available/traceable) should be counselled and written consent be obtained, preferably from both partners (if available/traceable), before initiating treatment with the medicine.

5.6.1.8 Men on treatment with the medicine must use barrier contraception and their female partners, if not pregnant, highly effective contraception, and if pregnant, a barrier type of contraceptive method, starting (indicate how many) days/weeks/months before they are put on treatment until (indicate how many) days/weeks/months after completion of treatment.

5.6.1.9 Males on treatment with the medicine must not donate sperm semen until (indicate how many) days/weeks/months after completion of treatment.

5.6.1.10 Females of child bearing age on treatment with this medicine should not donate ova until (indicate how many) days/ weeks/months after completion of treatment.

5.6.1.11 Females of child bearing age or who are pregnant, or planned to become pregnant, should not handle/prepare the medicine for patients in health care facilities/home care patients or own family members at home. If this is unavoidable, they should use appropriate protection to prevent or minimise the risk of being exposed to the medicine e.g. use appropriate eye protection gear, hand washing, gloves, face masks and make use of a laminar flow cabinet.

5.6.11.2 Mothers breastfeeding their babies or administer their own expressed breastmilk to their babies must stop breastfeeding or administering their own expressed breastmilk to their babies, if they are to be treated with the medicine until (indicate how many) weeks/months after completion of treatment. The medicine and/or its metabolite(s) is/are excreted in breastmilk and harm to the breastfeeding baby is confirmed or cannot be excluded OR it is unknown whether the medicine and/or its metabolites is/are excreted in breastmilk and harm to the breastfeeding baby cannot be excluded. Mothers must not donate their breastmilk to a breastmilk bank whilst on treatment with the medicine until (indicate how many) weeks/months after completion of treatment

6 TEMPLATE OF SUBHEADINGS TO BE INCLUDED IN THE HUMAN REPRODUCTION SECTION OF THE PROFESSIONAL INFORMATION OF THE MEDICINE

Brief / concise descriptions should be given, of findings, where relevant, under each subheading

6.1 PREGNANCY SAFETY RISK CATEGORY

State the pregnancy safety risk category

6.2 PREGNANCY

Indicators of harm/potential harm to the conceptus/embryo/developing foetus, in any trimester of pregnancy or a particular trimester of pregnancy (animal and/or human data where relevant)

6.3 LABOUR AND DELIVERY PROCESS / BIRTH OF THE BABY

Indicators of interference with labour and/or delivery process / birth of the baby (animal and /or human data where relevant)

6.4 CONDITION OF BABY AT BIRTH AND THERE AFTER

Indicators of an impact on the condition of the baby / wellness of the baby at birth or later

6.5 BREAST MILK

*Indicators that the medicine and/or its metabolites interfere/may interfere with the regulation/control of breast milk production and/or is excreted in breast milk and whether harm/potential harm in the breastfeeding baby has been confirmed/cannot be excluded OR it is unknown whether the medicine and/or its metabolite(s) is/are excreted in breast milk and harm/potential harm to the breastfeeding infant cannot be excluded OR the medicine and/or its metabolites is/are not excreted in breast milk and there is no risk of harm to the breastfeeding baby (animal and/or human data where relevant).

6.6 BREASTFEEDING

State whether breastfeeding is safe or breastfeeding should be stopped whilst the mother is on treatment until (indicate how many) weeks/months after completion of treatment

6.7 MALE/FEMALE REPRODUCTION ORGANS AND FERTILITY

Indicators of harm/potential harm to one or more reproduction organs (animal and/or human data where relevant) and the impact thereof on sexual behaviour / interest / libido and fertility and the ability to procreate/conceive. State whether fertility is impaired, whether it is reversible (partially reversible or reversible to pre-treatment fertility status) or irreversible (permanent). If fertility is impaired but reversible, indicate how many weeks/months after completion of treatment will fertility be back to the pre-treatment status

6.8 MALE/FEMALE CONTRACEPTION

Indicate type/method of contraception, how many days/weeks it should be initiated before treatment and for how many weeks/months should it be continued after completion of treatment with the medicine

6.9 INCLUSION OF PREGNANCY SAFETY RISK CATEGORY SPECIFIC PROPOSED STATEMENTS, WHERE RELEVANT, AS CONTAINED IN THE HUMAN REPRODUCTION GUIDANCE DOCUMENT UNDER EACH PREGNANCY SAFETY RISK CATEGORY

7 SELECTIVE RISK MINIMISATION MEASURES/REQUIREMENTS FOR CONSIDERATION, WHERE RELEVANT, AS A CONDITION OF REGISTRATION, FOR A MEDICINE WHICH IS HARMFUL TO HUMAN REPRODUCTION AND PREGNANCY, TO ENSURE ITS SAFE USE (THESE MEASURES/REQUIREMENTS ARE NOT TO BE INCLUDED IN THE HUMAN REPRODUCTION SECTION OF THE PROFESSIONAL INFORMATION OF THE MEDICINE)

7.1 General Information

7.1.1 Risk minimisation requirements/measures/activities/interventions as components of a broader Risk Management Plan (RMP), usually impose some measure of burden and responsibility on health care professionals/medical practitioners, pharmacists, health care facilities, pharmacies and patients.

7.1.2 Risk minimisation requirements / measures / activities / interventions are part of a more comprehensive risk management plan/programme, designed to minimise the risk and maximise the benefits of a particular medicine to a patient in need to be treated with a medicine with an unfavourable benefit to harm risk or where the benefit to harm risk is borderline or inconclusive based on the available data sources.

7.2 Selective risk minimisation requirements /measures / activities / interventions to be considered, where relevant.

7.2.1 This document will only address certain risk minimisation requirements /measures / activities or interventions relevant to consider for a medicine which may have, or does have, a negative impact on aspects of human reproduction, pregnancy and lactation/breastfeeding, but is needed for treatment of female/male patients with conditions/diseases or disorders where treatment cannot be delayed, are unavoidable or for which a safe or safer alternative medicine is not available, cannot be tolerated, has failed or is contraindicated.

7.2.2 Submissions for approval of medicines that fall into any of the pregnancy safety risk categories, except for the insignificant pregnancy safety risk category, must have a relevant Risk Management Plan as part of the submission. Such a plan should include professional information of the medicine and patient information, with measures to minimise risks and to ensure safe use of the medicine including a counselling, communication and implementation plan with defined time lines where needed/relevant.

7.2.3 **Requirements/measures/activities to ensure safe use of a medicine that is harmful for human reproduction, pregnancy and lactation/breastfeeding, may include one or more or all of the following:**

7.2.3.1 It may be a requirement that medical practitioners / pharmacists / health care professionals should receive additional educational material (e.g. guide / manual for health care professionals), training or certification before they are allowed to prescribe / dispense the medicine. Health care professionals may also be required to keep updated records of their patients on treatment with the medicine, including amongst others, their full contact details.

7.2.3.2 It may be a requirement that each patient should receive a lay language information booklet explaining, amongst others, the potential harms and benefits of the medicine relating to human reproduction, fertility, pregnancy and breastfeeding, how it should be used, the importance to adhere to the directions of their medical practitioner regarding the treatment and where to go to (health facility) or who to phone (24 hour phone number) in case of problems/adverse effects encountered by them.

7.2.3.3 It may be a requirement that patients should receive appropriate counselling regarding all relevant aspects of the medicine, the treatment programme and that the patient should complete and sign an informed consent form, and if not included in the consent form, a separate acknowledgement form, which clearly states that the benefits and the risks of treatment with the medicine were explained to him/her, that he/she has truly understood the information, and that he/she had adequate time to ask questions and that they received satisfactory answers to all their questions.

A patient card, containing particular core information, may be required to be issued to the patient to present at the point of dispensing or at appointments/visits to health care facilities.

7.2.3.4 It may be a requirement that pharmacists, medical practitioners and/or health care facilities and pharmacies are to be certified/licensed to allow them to keep supplies/prescribe and dispense the medicine.

7.2.3.5 It may be a requirement that permission to keep a supply of the medicine and dispense the medicine may be restricted to only a few health care facilities in a particular geographical area e.g. only a few pharmacies or a hospital.

7.2.3.6 It may be a requirement that the medicine may only be dispensed to patients in person (ID document needed or another form of identity verification), or who are in position of certain documents e.g. a prescription, patient card, appropriate laboratory test results, educational material in lay language, or a letter from the medical practitioner, co-signed by the patient, that he/she was counselled on the benefits and harms of the medicine.

7.2.3.7 It may be a requirement that each patient on treatment with the medicine, should consent in writing that he/she has accepted to be subjected to certain monitoring modalities during treatment, and to honour the scheduled follow up appointments / visits made for them for the duration of treatment.

7.2.3.8 It may be a requirement that each patient on treatment with the medicine should consent / give permission in writing, to be enrolled in a registry designed to collect appropriate information regarding the treatment and the outcomes thereof.

7.2.3.9 It may be a requirement that the label of a medicine that is known to be harmful in pregnancy and lactation, should have a marker on the label to ensure easy identification thereof e.g. by means of a pictogram/picture on the label or other identification marker

8 ADDENDUM: ASPECTS OF CONTRACEPTION RELAVANT TO THIS GUIDELINE

8.1 Effectiveness of contraception

Each contraceptive method has a failure rate or percentage of women who can expect to become pregnant within the first year of use of their chosen contraceptive method. Effectiveness rates of a contraceptive method can be viewed in two ways:

8.1.1 "With perfect use" (theoretical effectiveness): This is how well a given contraceptive method will work when used correctly and consistently as described in the dosage and directions for use of the specific contraceptive method (the perfect user).

8.1.2 "With typical use" (use effectiveness): This is how well a given contraceptive method will work in actual use situations including occasional, inconsistent or incorrect use based on human error and non-ideal factors (not always and consistently used as described in the dosage and directions for use of the specific contraceptive method). Many women are "typical" users of their chosen contraceptive method rather than "perfect" users and thereby decreasing the effectiveness of their chosen contraceptive method.

8.2 "Typical" vs "Perfect" users

Many women of child bearing age are more likely to be "typical" users of their chosen contraceptive method rather than "perfect" users. Therefore to prevent an unintentional pregnancy in a woman who is regarded as a "typical" user, consideration should be given to the use of two acceptable contraceptive methods such as a hormonal method by the female partner plus a barrier method (male condom with spermicide) by the male partner. Female condoms and male condoms should not be used simultaneously, as they can adhere to each other and cause slippage or breakage of one or both barrier devices and thereby decreasing the contraceptive effectiveness

8.3 Highly effective contraception/contraceptive methods

8.3.1 A highly effective contraceptive method has a low failure rate (e.g. <1% per year) when used consistently and correctly as per dosage and directions for use of the specific contraceptive method (perfect use/user).

Examples of "highly effective" contraceptive methods with a failure rate of <1% per year include reversible hormonal implants, intrauterine devices (hormonal or non-hormonal), oral hormonal contraceptives (progestin only, oestrogen/progesterone combinations), hormonal patch, hormonal ring, abstinence and sterilisation.

Abstinence and sterilisation (female/male) are usually not considered to be an option for protection to become pregnant during a course of treatment with a medicine that may be harmful to the conceptus/embryo or developing foetus. The risk with abstinence is that it may be difficult to abstain from all sexual activities for the duration of treatment and sterilisation is an unlikely option because of the irreversibility thereof.

Despite the fact that the female partner is a "perfect" user of her highly effective contraceptive method, partners and/or the medical practitioner may decide it is in their best interest that the male partner should also use a barrier contraceptive.

8.3.2 "Typical" contraceptive method users: Women who are considered to be "typical" contraceptive method users should be protected against pregnancy during a treatment course with a medicine harmful to the conceptus/embryo or developing foetus, by choosing a highly effective contraceptive method, after counselling of the woman, which effectiveness is less dependable on her lifestyle / actions / behaviour such as a hormonal implant or suitable intrauterine device. If this is not possible both partners should use a contraceptive method. The female partner should use a highly effective contraceptive method of her choice and the male partner a barrier contraceptive (male condom with spermicide).

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10 UPDATE HISTORY

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Nov 2017	First publication for comment	v1, May 2018
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