令和４年１月 24 日
令和３年度医薬品等安全対策調査会
資料１－３

海外添付文書の記載状況

国	製品名 （添付文書の版）	記載状況（網かけ部は、投与前の妊娠していないことを確認する方法に関する記載）
米国	Plan B One-Step （2009 年 7 月版）	4 CONTRAINDICATIONS Plan B One-Step is contraindicated for use in the case of known or suspected pregnancy. 5 WARNINGS AND PRECAUTIONS 5.2 Existing Pregnancy Plan B One-Step is not effective in terminating an existing pregnancy. 5.5 Physical Examination and Follow-up A physical examination is not required prior to prescribing Plan B One-Step. A follow-up physical or pelvic examination is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking Plan B One-Step. 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Many studies have found no harmful effects on fetal development associated with long-term use of contraceptive doses of oral progestins. The few studies of infant growth and development that have been conducted with progestin-only pills have not demonstrated significant adverse effects.
英国	Levonelle One Step 1500 microgram tablet （2018 年 11 月版）	4.3 Contraindications （関連記載なし） 4.6 Fertility, pregnancy and lactation Pregnancy Levonelle One Step should not be given to pregnant women. It will not interrupt a pregnancy. In the case of continued pregnancy, limited epidemiological data indicate no adverse effects on the fetus but there are no clinical data on the potential consequences if doses greater than 1.5 mg of levonorgestrel are taken (see section 5.3.). 5.3 Preclinical safety data Animal experiments with levonorgestrel have shown virilisation of female fetuses at high doses. Preclinical data from conventional studies on chronic toxicity, mutagenicity and

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		carcinogenicity reveal no special hazard for humans, beyond the information included in other section of the Summary of Product Characteristics.
フランス （邦訳）	ノルレボ錠 1.5mg （2019 年 2 月版）	4.3. 禁忌 （関連記載なし） 4.6. 受胎能、妊娠及び授乳 妊娠 本剤が進行中の妊娠を中断することはない。 本避妊法が失敗して妊娠が継続した場合、プロゲスチンは胎児奇形リスクをもたらさないことが疫学研究の結果により示されている。 レボノルゲストレルを 1.5 mg を超える用量で服用した場合の児への影響は知られていない。 5.3. 前臨床安全性データ ヒトにおけるリスクは従来の安全性薬理試験、反復投与毒性試験、遺伝毒性試験、発癌性試験に由来する非臨床データにより、本製品特性概要の他の項に記載されたリスク以外のその他のリスクは示唆されていない。動物データにより、高用量のレボノルゲストレル投与後に雌胎仔の雄性化が示されている。
ドイツ	Levonorgestrel STADA 1.5mg tablets （2016 年 7 月版）	4.3 Contraindications (関連記載なし) 4.6 Fertility, pregnancy and lactation Pregnancy This medicinal product cannot interrupt an ongoing pregnancy. In case of failure of this contraceptive mean with persisting pregnancy, epidemiological studies indicate no malformative effects of progestins on foetus. Nothing is known on the consequences for the child if doses higher than 1.5 mg levonorgestrel are taken. 5.3 Preclinical safety data Nonclinical data reveal no special hazard for humans, beyond the information included in other sections of the SPC. Animal experiments with levonorgestrel have shown virilisation of female foetuses at high doses.
カナダ	PLAN B Levonorgestrel	CONTRAINDICATIONS Women with known or suspected pregnancy. The method is not to be used by a woman who is

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	Tablet 1.5 mg （2018 年 4 月版）	pregnant due to a previous act of intercourse, especially if there is recent abnormal bleeding, a pregnancy test should be performed before taking Plan B. WARNINGS AND PRECAUTIONS General Plan B® is not an abortifacient and should not be taken by pregnant women, as it will not be effective. Sexual Function/Reproduction Suspected Pregnancy: A pregnancy test is warranted if pregnancy is suspected. Women should be counselled to abstain from sexual intercourse or use an alternative contraceptive method until the onset of their next normal menstrual period. If a normal menstrual period is delayed beyond 1 week, the patient's pregnancy status should be confirmed with a pregnancy test and follow-up with a health professional. Special Populations Pregnant Women: Plan B® is not an abortifacient and should not be taken by pregnant women, as it will not be effective. Studies involving women who have taken combined oral contraceptives containing levonorgestrel inadvertently during early pregnancy do not suggest that these drugs have an adverse effect on the fetus and there is no evidence that Plan B® (levonorgestrel 1.5 mg tablet) taken as an emergency contraceptive would have an adverse effect on an established pregnancy. However, there are insufficient data to rule out the possibility of adverse effects on the fetus if Plan B® is used after a woman is already pregnant or in cases of method failure. TOXICOLOGY Reproductive Toxicity: A large number of reproductive toxicity studies were performed by repeat dose administration to evaluate the effects on mating fertility, fecundity, post-treatment recovery of fertility, effects on the estrous cycle, claudogenic effects as well as classic Segment I, II, and III reproductive studies. Of greatest possible relevance to emergency contraception are the studies of recovery of fertility and birth defects. In a study in mice treated with up to 50x the human contraceptive dose, no irreversible impairment of fertility was noted.

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		Segment II studies were given by repeat dose during organogenesis. At the levels required to maintain pregnancy, virilizing effects were noted and were considerably greater than those of progesterone. Two of 439 fetuses from dams treated at these levels of norgestrel were deformed; one fetus from a dam treated with norgestrel 3 mg subcutaneously had incomplete spinal closure and one fetus from a dam treated with norgestrel 3 mg orally had a poorly developed cranium. The 88 control fetuses were normal. Occasional deformities appeared in the other progestogen groups, and were more frequent from spayed mothers. In a study where norgestrel was given subcutaneously from Days 16 to 19 of gestation, potency in producing virilization in female fetuses was found to be nearly equal to testosterone propionate and three times greater than norethindrone acetate. Histological examination showed that norgestrel 0.1 mg/day subcutaneously was effective, while 10 mg/day orally was ineffective. For a macroscopically detectable increase in ano-genital distance, 3 mg/day subcutaneously was required.
オーストラリア	NorLevo-1 levonorgestrel 1.5 mg tablet （2020年1月版）	4.3 CONTRAINDICATIONS NorLevo-1 should not be given to pregnant women. If menstrual bleeding is overdue, if the last menstrual period was abnormal in timing or character or if pregnancy is suspected for any other reason, pregnancy should be excluded (by pregnancy testing or pelvic examination) before treatment is given. If a woman has had unprotected intercourse more than 72 hours earlier in the same menstrual cycle conception may have already occurred. Treatment with NorLevo-1 following the second act of intercourse may therefore be ineffective in preventing pregnancy. While the consensus is that levonorgestrel is not teratogenic, no guarantee can be given that pregnancy will result in a normal baby. 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE Precautions before use Exclude pregnancy if suspected clinically. Breast or pelvic examinations are not routinely necessary. Perform such examinations only if indicated by the patient's history. Blood pressure may be measured before recommending NorLevo-1. An elevated blood pressure is not a contraindication to treatment but indicates the need for further investigation.

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		No routine laboratory testing is required. 4.6 FERTILITY, PREGNANCY AND LACTATION Use in pregnancy - Pregnancy Category D※ NorLevo-1 is not to be used during an existing or suspected pregnancy. Research has found no significant effects on fetal development associated with the long-term use of contraceptive doses of combined oral steroids before pregnancy or taken inadvertently during early pregnancy. There have been an insufficient number of pregnancies in patients using levonorgestrel only oral contraceptives to rigorously evaluate the potential for developmental toxicity; however, based on the combined oral contraceptive experience, an increase in abnormalities is not expected. If taken by the mother at or after eight weeks postconception, progestogens such as levonorgestrel can cause virilisation of the female fetus. This is a dose dependent effect. Prior to eight weeks postconception, they have no virilising effects. There are no studies of the effect of the high levonorgestrel doses used in levonorgestrel 1.5 mg tablets on pregnancy and embryo/fetal development.

※公表されている最新の添付文書（2020 年 1 月版）ではカテゴリ D に分類されているが、オーストラリア医療製品管理局（TGA）の最新（2021 年 4 月 15 日版）の妊娠データベース（www.tga.gov.au/prescribing-medicines-pregnancy-database）ではカテゴリ B3 に分類されている。

カテゴリ B3：限られた数の妊婦および妊娠可能な年齢の女性のみが服用したことのある薬剤で、奇形の発生頻度の増加や、ヒトの胎児に対する直接的または間接的な有害作用が観察されていないもの。動物を用いた研究では、胎児へのダメージの発生が増加するという証拠が示されているが、その重要性はヒトでは不確かであると考えられる。

カテゴリ D：ヒトの胎児の奇形や不可逆的な損傷の発生率を増加させた、またはその疑いがある、あるいはその可能性がある薬剤。また、これらの薬剤は薬理学的にも悪影響を及ぼす可能性がある。