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Summary of Investigation Results

Chlormadinone acetate
Medroxyprogesterone acetate

December 17, 2024

Non-proprietary name

a. Chlormadinone acetate

b. Medroxyprogesterone acetate

Brand name (marketing authorization holder)

See attachment.

Japanese market launch

See attachment.

Indications

See attachment.

Summary of revisions

1. A cautionary statement regarding meningioma should be added to the 8. IMPORTANT PRECAUTIONS section.
2. “Patients with meningioma or a history of the disease” should be added to the 9.1 Patients with Complication or History of Diseases, etc. section of 9 PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS.
3. The results of an overseas epidemiological study should be added to the 15.1 Information Based on Clinical Use section in 15. OTHER PRECAUTIONS.

Investigation results and background of the revision

The published literature on meningioma after administration of chlormadinone acetate or medroxyprogesterone acetate and cases involving menigioma were evaluated. As a result of

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consultation with expert advisors regarding the necessity of revision of PRECAUTIONS, the MHLW/PMDA concluded that revision of PRECAUTIONS was necessary for the following reasons, although the causal relationship of chlormadinone acetate or medroxyprogesterone acetate to meningioma was not clear:

•An overseas epidemiological study (Noémie R., et al.: BMJ, 2024; 384: e078078) indicated a risk of occurrence of meningioma in females who received chlormadinone acetate or medroxyprogesterone acetate.

•Adverse reactions have been reported in males who presented with meningioma following administration of chlormadinone acetate.

•In adverse reaction reports, cases in which meningioma shrunk after discontinuation of chlormadinone acetate or medroxyprogesterone acetate have been reported.

Reference: Number of cases* and patient mortalities involving meningioma reported in Japan and overseas

a. A total of 2 cases have been reported in Japan to date.
   No patient mortalities have been reported in Japan to date.
b. One case has been reported in Japan to date.
   No patient mortalities have been reported in Japan to date.
a. A total of 57 cases have been reported overseas to date.
   No patient mortalities have been reported overseas to date.
b. A total of 39 cases have been reported overseas to date.
   No patient mortalities have been reported overseas to date.

*Cases collected in the PMDA's database for adverse drug reactions, etc. reports
Cases with “meningioma” in MedDRA PT were retrieved.
Of note, the possibility of a causal relationship between the drugs and the events was not evaluated.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

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Attachment

No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Therapeutic category, etc.	Indications
a.	Chlormadinone acetate	Prostal Tablets 25 and the others	Aska Pharmaceutical Co., Ltd. and the others	September 1981	Agents for treatment of prostatic hyperplasia/cancer	Prostatic hyperplasia, prostate cancer Note that, for patients with prostate cancer accompanied by metastases, this drug is used when the disease is refractory or intolerant to other therapies.
		Prostal-L-Tablets 50 mg	Aska Pharmaceutical Co., Ltd.	August 1990 (Date of Japanese market launch of “Prostal-L-Tablets”)	Extended-release agents for treatment of prostatic hyperplasia	Prostatic hyperplasia
		Lutoral tablets 2 mg	Fuji Pharma Co., Ltd.	April 1965	Oral gestagen preparations	Amenorrhoea, abnormal menstrual cycle (oligomenorrhoea, hypermenorrhoea) or adjusting the start of controlled ovarian stimulation in assisted reproductive technology, abnormal amount of menstrual blood loss (hypomenorrhoea, hypermenorrhoea), dysmenorrhoea, functional uterine bleeding, ovarian failure, infertility due to luteal phase deficiency or luteal support as part of assisted reproductive technology for infertile women

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Therapeutic category, etc.	Indications
b.	Medroxyprogesterone acetate	Provera Tablets 2.5mg and the others	Pfizer Japan Inc. and the others	January 1963 (Date of approval of “Provera”)	Oral gestagen preparations	Amenorrhoea, abnormal menstrual cycle (oligomenorrhoea, hypermenorrhoea), abnormal amount of menstrual blood loss (hypomenorrhoea, hypermenorrhoea), functional uterine bleeding, infertility due to luteal phase deficiency, threatened abortion/premature labour, habitual abortion/premature labour
		Hysron Tablets 5 and the others	Kyowa Kirin Co., Ltd. and the others	July 1967	Oral gestagen preparations	Amenorrhoea, abnormal menstrual cycle (oligomenorrhoea, hypermenorrhoea) or adjusting the start of controlled ovarian stimulation in assisted reproductive technology, abnormal amount of menstrual blood loss (hypomenorrhoea, hypermenorrhoea), functional uterine bleeding, infertility due to luteal phase deficiency, threatened abortion/premature labour, habitual abortion/premature labour, prevention of premature ovulation during controlled ovarian stimulation
		Hysron-H Tablets 200 mg and the others	Kyowa Kirin Co., Ltd. and the others	May 1987 (Date of Japanese market launch of “Hysron-H 200”)	antineoplastic oral gestagen preparations	•Breast cancer •Corpus uteri carcinoma (endometrial cancer)

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