Medicines Adverse Reactions Committee

Meeting date	**5 December 2019**	Agenda item	3.2.3
Title	**Cyproterone acetate and the risk of hepatic toxicity**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent Cyproterone	**Medicines** Procur tablets Siterone tablets	**Sponsors** Douglas Pharmaceuticals Limited REX Medical Ltd	
Funding	Siterone 50 mg and 100 mg are funded		
Previous MARC meetings	Cyproterone use as a contraceptive has been discussed previously at the following meeting: – 171st Meeting — 14 September 2017 Risks of severe depression, anxiety and suicidal ideation with hormonal contraceptives.		
Prescriber Update	There have been articles regarding the risk of VTE when cyproterone is used as a contraceptive.		
Schedule	Prescription medicine		
Usage data	See section 2.4		
Advice sought	**The Committee is asked to advise whether:** – The data sheets for cyproterone tablets should be updated regarding the risk of hepatic toxicity. – This topic requires further communication other than MARC's Remarks in *Prescriber Update*.		

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1.0 PURPOSE

The Centre for Adverse Reactions Monitoring (CARM) received a case report regarding a 44-year-old woman who was treated with cyproterone [redacted]. The dose was 50 mg every day. After developing symptoms such as abdominal pain, lethargy, loose, green stools, dark urine and jaundice, severe hepatitis was diagnosed. Cyproterone was the suspected cause of the hepatitis. See section 3.5 for further information.

The data sheets for cyproterone includes information about direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, but states that it has been reported in patients treated with 200 – 300 mg cyproterone acetate and mostly in men with prostatic cancer.

Considering that cyproterone is also indicated for women and there is a potential risk of hepatic reactions also for women and with lower doses, the wording in the data sheets may not be accurate. Therefore, Medsafe considers that this safety concern should be reviewed by the MARC. Note that this review is not relevant to contraceptives use as these medicines contain far less cyproterone.

2.0 BACKGROUND

2.1 Cyproterone

Cyproterone is available as cyproterone acetate (CPA) tablets in New Zealand under the names Procur and Siterone. There are two strengths of the tablets: 50 mg and 100 mg. Cyproterone is also available in combination with ethinylestradiol, but the combination is not relevant for this review.

2.1.1 Indications

Men: Antiandrogen treatment in inoperable carcinoma of the prostate
Reduction of drive in sexual deviations.

Women: Severe signs of androgenization, e.g. very severe hirsutism in the female, severe androgenetic alopecia, often attended by severe forms of acne and/or seborrhoea (1, 2).

2.1.2 Dosing

Men

- Antiandrogen treatment in inoperable carcinoma of the prostate
    - to eliminate the effect of adrenocortical androgens after orchiectomy: one 100 mg tablet once or twice daily (100-200 mg).
    - Without orchiectomy: one 100 mg tablet twice to three times daily (200-300 mg).
    - Treatment should not be interrupted, nor the dosage reduced after improvement or remissions have occurred.
    - To reduce the initial increase of male sex hormones in treatment with LH-RH agonists: Initially one 100 mg tablet twice daily (200 mg) alone for 5 - 7 days followed by one 100 mg tablet twice daily (200 mg) for 3 - 4 weeks together with an LH-RH agonist in the dosage recommended by the manufacturer.
    - To eliminate the effect of adrenocortical androgens in treatment with LH-RH agonists: Continuation of the antiandrogen therapy with one 100 mg tablet once to twice daily (100 – 200 mg).

- Reduction of drive in pathologically altered or increased sexuality
    - Generally, the treatment is started with one 50 mg tablet twice daily. It may be necessary to increase the dose to two 50 mg tablets twice daily or even two 50 mg tablets three times daily for a short period of time. When a satisfactory result is achieved, an attempt should be made to maintain the therapeutic effect with the lowest possible dose.

Women

One tablet of 100 mg is to be taken daily with some liquid after a meal from the 1st to the 10th day of the menstrual cycle (for 10 days). Following clinical improvement, the daily dose can be reduced. In addition, the women receive a progestogen-oestrogen preparation (1 tablet ethinylestradiol 0.035 mg/cyproterone acetate 2 mg daily), e.g. from the 1st to the 21st day of the cycle, to provide the necessary contraceptive protection and to stabilise the cycle. After that there is a 7-day tablet free interval.

In postmenopausal or hysterectomised patients, cyproterone may be administered alone. According to the severity of the complaints, the average dose should be one to ½ tablet 50 mg once daily for 21 days, followed by a 7-day tablet-free interval (1, 2).

Comments: Note that in the data sheet for Procur, dosage for men regarding the indication Reduction of drive in pathologically altered or increased sexuality and for women, is given as number of tablets per day but it is not clear if these tablets are 50 mg or 100 mg, which is very confusing. It is also not clear which strength they mean in the dosing to reduce flare at initiation of treatment with LH-RH agonists.

2.1.3 History and pharmacodynamics

CPA was first synthesised in 1961 and was introduced in Europe in 1964 (3). Cyproterone is a steroid hormone preparation that inhibits the influence of androgensin both men and women.

The direct antiandrogenic effect results in a blockage of the binding of dihydrotestosterone (DHT) to prostatic cancer cells and a negative feedback on hypothalamic-pituitary axis by inhibition of luteinizing hormone (LH) secretion, leading to decreased testosterone production.

CPA is also used as an antiandrogen to treat androgen-dependent skin and hair conditions such as acne, seborrhea, hirsutism (excessive hair growth), scalp hair loss, and hidradenitis suppurativa in women..

In men, treatment with PROCUR reduces sexual drive and potency and gonadal function is inhibited. These changes are reversible following discontinuation of the therapy.

In women, hirsuitism is reduced, as well as androgen-dependent alopecia and elevated sebaceous gland function. During treatment, ovarian function is reduced.

Cyproterone exerts a progestin-like effect by activating the progesterone receptor (PR). By activating the PR, CPA also has antigonadotropic effects and can inhibit fertility and suppress sex hormone production in both men and women.

Cyproterone at a lower dose is used together with ethinylestradiol for the treatment of signs of androgenisation in women, such as severe acne where prolonged oral antibiotics or local treatment alone has not been successful, or idiopathic hirsutism of mild to moderate degree. (1, 4, 5).

2.1.4 Contraindications and warnings

Cyproterone is contraindicated in the following circumstances (1, 2):

- Hypersensitivity to any of the ingredients
- Pregnancy
- A history of jaundice or persistent itching during a previous pregnancy
- A history of herpes in pregnancy
- Lactation
- Liver diseases
- Previous or existing liver tumours (in carcinoma of the prostate only if these are not due to metastases)
- Meningioma or a history of meningioma
- Wasting diseases (with the exception of carcinoma of the prostate)
- Dubin-Johnson syndrome (a rare, benign disorder with increase of conjugated bilirubin in the serum and causing a black liver due to deposition of a pigment similar to melanin)
- Rotor syndrome
- Severe chronic depression
- Previous or existing thromboembolic processes
- Severe diabetes with vascular changes
- Sickle-cell anaemia

General warnings and precautions for use from the data sheets (1, 2):

- The drive-reducing effect can be diminished by alcohol.
- Cyproterone should not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and the still unstabilised axes of endocrine function cannot be ruled out.
- Liver function, adrenocortical function and red blood-cell count should be checked regularly during treatment.
- Liver toxicity see section 2.3.1.
- The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone.
- Strict medical supervision of diabetic patients.
- A sensation of shortness of breath may occur in individual cases under high dosed treatment
- In extremely rare cases, the occurrence of thromboembolic events has been reported in temporal association with the use of cyproterone although a causal relationship seems to be questionable. Rarely cases of osteoporosis have also been reported.
- Before the start of therapy, a thorough general medical and gynaecological examination should be carried out in women and pregnancy must be excluded.

Contraindications, warnings and precautions to ethinylestradiol need to be considered if cyproterone is used for combination treatment.

2.1.5 Adverse reactions

The most frequently observed adverse drug reactions (ADRs) in patients receiving cyproterone acetate are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

The most serious ADRs in patients receiving cyproterone acetate are hepatic toxicity, benign and malignant liver tumours which may lead to intra-abdominal haemorrhage and thromboembolic events. Table 1 shows the adverse reactions listed in the Procur data sheet, including incidences (1).

Table 1: Adverse reactions listed in the Procur data sheet.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

- Very rare: Benign/malignant liver tumours, may lead to life threatening intra-abdominal haemorrhage.
- Not known: Meningiomas (see section 2.1.4).

Blood and the lymphatic system disorders

- Not known: Anaemia during long term treatment.

Immune system disorders

- Rare: Hypersensitivity reactions.

Endocrine disorders

- Not known: Suppression of adrenocortical function.

Metabolism and nutrition disorders

- Common: Changes in bodyweight during long term treatment.

Psychiatric disorders

- Common: depressive moods and restlessness.
- Not known: Diminished vitality.

Vascular disorders

- Not known: Thromboembolic events (see section 2.1.4).

Respiratory, thoracic and mediastinal disorders

- Common: dypsnoea.

Hepato-biliary disorders

- Common: Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200-300 mg cyproterone acetate.

Skin and subcutaneous tissue disorders

- Uncommon: Rash.
- Not known: Reduction of sebum production leading to dryness of the skin and improvement of existing acne vulgaris has been reported as well as changes to scalp- and body hair

Musculoskeletal and connective tissue disorders

- Not known: Osteoporosis (due to long-term androgen deprivation).

Reproductive system disorders

<u>Inhibition of spermatogenesis</u>

- Very common: Sperm count, and volume of ejaculate reduced. Infertility is usual, and there may be azoospermia after 8 weeks. There is usually slight atrophy of the seminiferous tubules. Have been shown to be reversible but if spermatogenesis can recover even after very long treatment is not yet known.
- Not known: In women, ovulation is inhibited when combined with estrogen/progestogen tablets, so that a state of infertility exists. In addition, a feeling of tension in the breasts may occur.

<u>Gynaecomastia</u>

- Common: Gynaecomastia (sometimes combined with tenderness to touch of the mamillae) which usually regresses after withdrawal of the preparation.
- Rare: Galactorrhoea and tender benign nodules have been reported. Symptoms mostly subside after discontinuation of treatment or reduction of dosage.

General disorders and administration site conditions

- Common: Hot flushes, sweating, fatigue and lassitude.

Comment: The Siterone data sheet does not include frequencies and is not as detailed. The following adverse reaction is not listed in the Siterone data sheet:
Psychiatric disorders: Diminished vitality.

2.1.6 Pharmacokinetics

Following oral administration, cyproterone acetate is completely absorbed over a wide dose range. The ingestion of 50 mg of cyproterone acetate gives maximum serum levels of about 140 ng/ml at about 3 hours. Thereafter drug serum levels decline during a time interval of typically 24 to 120 h, with a terminal half-life of 43.9 ± 12.8 h. The total clearance of cyproterone acetate from serum was determined to be 3.5 ± 1.5 ml/min/kg. Cyproterone acetate is metabolised by various pathways, including hydroxylation and conjugation. The main metabolite in human plasma is 15β-hydroxy derivative.

A proportion is excreted unchanged with bile fluid. Most of the dose is excreted in the form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with a half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days).

Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 – 4 % of total drug levels are unbound. Because protein binding is nonspecific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

Cyproterone has a slow metabolism. According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, an accumulation of cyproterone acetate by a factor of about 3 can be expected in the serum during repeated daily administration.

The absolute bioavailability of cyproterone acetate is almost complete (88 % of dose) (1, 2).

2.2 Drug induced liver injury such as hepatitis

Drug induced liver injury (DILI) has an estimated annual incidence between 10 and 15 per 10,000 to 100,000 persons exposed to prescription medications. DILI accounts for approximately 10 percent of all cases of acute hepatitis. There are several different mechanisms and symptoms of DILI. DILI is also the most frequently cited reason for withdrawal of medicines from the marketplace.

DILI may not be detected prior to drug approval because it is too rare. It has been suggested that for every 10 cases of alanine aminotransferase (ALT) elevation (>10 times the upper limit of normal) in a clinical trial, there will be one case of more severe liver injury that develops once the drug is widely available.

DILI is often characterized by the type of hepatic injury: hepatocellular (cytotoxic) injury (hepatitis), cholestatic injury (cholestasis), or a mixed picture (which includes features of both hepatocellular injury and cholestatic injury) (6).

Symptoms of drug-induced hepatitis may include abdominal pain, tiredness and weakness, fever, nausea, vomiting, lack of appetite, dark urine, pale or clay-colored stools and jaundice (7).

Several risk factors have been associated with the development of DILI. In general, adults are at higher risk for DILI than children and women may be more susceptible than men, which may in part be due to their generally smaller size.

Over 1000 medications and herbal products have been implicated in the development of DILI, and the list continues to grow (6).

The mechanisms of CPA-induced DILI are not clearly understood. Immunological reactions have been hypothesized. However, a direct toxic effect of the drug itself or its metabolites may occur as well (3).

2.3 Data sheets cyproterone

2.3.1 New Zealand

The last update of the data sheet for Procur was 22 February 2019 (1). The last update of the data sheet for Siterone was 19 September 2018 (2).

The relevant sections of the NZ data sheets for cyproterone are summarised below.

- Section 4.3 Contraindications

Liver diseases.

- Section 4.4 Special warnings and precautions for use

During treatment, liver function, adrenocortical function and the red blood-cell count should be checked regularly.

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200 – 300 mg cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

As with other sex steroids, benign and malignant liver changes have been reported in isolated cases. In very rare cases, liver tumours may lead to life threatening intra-abdominal haemorrhage. This is also listed in 4.8 Undesirable effects for Procur but not for Siterone. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic considerations.

- Section 4.8 Undesirable effects

Procur: Hepato-biliary disorders

Common: Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200-300 mg cyproterone acetate.

Siterone: Hepato-biliary disorders

Hepatic toxicity including jaundice, hepatitis, hepatic failure (sometimes fatal)

Section 5.3, Preclinical safety data, includes a text on genotoxicity. Cyproterone has been shown to be capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes. The DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. One in vivo consequence of cyproterone acetate treatment was the increased incidence of focal, possibly preneoplastic liver lesions in which cellular enzymes were altered in female rats. The clinical relevance of these findings is presently uncertain.

Comment: The data sheet states that cases of direct hepatic toxicity has been reported in patients treated with 200 – 300 mg cyproterone acetate and most reported cases are in men with prostate cancer. There are more cases reported for men, but this formulation of the text may be of limited value if reactions also occur in women and they are not monitored as the text implies that hepatic toxicity does not occur.

2.3.2 UK

Cyproterone monotherapy is only indicated for treatment of men. There are 50 mg and 100 mg tablets available. The SPC includes the following text:

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, has been observed in patients treated with cyproterone. At dosages of 100 mg and above cases with fatal outcome have also been reported. Most reported fatal cases were in men with advanced prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment, regularly during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, Cyprostat should be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case Cyprostat should be continued only if the perceived benefit outweighs the risk.

In very rare cases benign and malignant liver tumours, which may lead to life-threatening intra-abdominal haemorrhage have been observed after the use of Cyprostat. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be considered in the differential diagnosis (8).

For treatment of women there are combination products of cyproterone acetate 2 mg and the oestrogen ethinylestradiol 35 micrograms which are administered for 21 days of a monthly cycle (same dose every day). The indication is treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in woman of reproductive age.

2.3.3 Sweden (EMA)

The last update of the SPC for Androcur 50 mg was 24 April 2017. The indications are different. For men it is reduction of drive in sexual deviations or hypersexuality and for women it is severe hirsutism in women of reproductive age. This means that the dosing for women is cyclic and sometimes combined with a contraceptive. There is no 100 mg tablet available.

The section 4.3 is divided into contraindications for men and for women. Liver disease is a contraindication in both groups. Section 4.4 is the same as in the NZ data sheet.

Section 4.8 is presented in 2 separate tables: undesirable effects during treatment of men and undesirable effects during treatment of women. For men "Liver toxicity such as jaundice, hepatitis and liver failure" is listed as a common adverse reaction (>1/100, <1/10). For women this adverse reaction is listed as an adverse reaction with no known frequency (9).

Table 2: Adverse reactions affecting the liver, from the SPC for Androcur in Sweden.

Men:

System organ class (MedDRA)	**Very common ≥1/10**	**Common ≥1/100 and < 1/10**	**Uncommon ≥1/1000 and < 1/100**	**Rare ≥1/10000 and < 1/1000**	**Very rare < 1/10**	**No known frequency**
		Hepatic toxicity, including jaundice, hepatitis, hepatic failure				

Women:

System organ class (MedDRA)	Very common ≥1/10	Common ≥1/100 and < 1/10	Uncommon ≥1/1000 and < 1/100	Rare ≥1/10000 and < 1/1000	Very rare < 1/10	No known frequency
						Hepatic toxicity, including jaundice, hepatitis, hepatic failure

Both texts states that the most common serious adverse reaction for Androcur is liver toxicity.

Comment: Dividing the adverse reactions section is one way to inform healthcare professionals that hepatic toxicity may occur in women, although not as commonly as in men. Note that cyproterone is cyclic treatment in Sweden.

2.3.4 US

Cyproterone is not approved in the US.

2.3.5 Canada

The last update of the product information for Androcur was 25 February 2011. In Canada the use of cyproterone is similar to the UK. The same text is included in the product information for Androcur 50 mg as in the cyproterone products in the UK. There is no 100 mg tablet. However, Androcur also has a Black Box Warning stating that hepatotoxicity with acute hepatic failure (see Hepatic/Biliary/Pancreas, Hepatotoxicity) are clinically significant adverse reactions (10).

2.3.6 Australia

There are several products available in Australia containing cyproterone alone or in combination with ethinylestradiol. Cyproterone 50 mg and 100 mg tablets are available. The 100 mg tablets are for use only in men. Cyprostat 50 mg product information was updated 26 October 2017. The indications are:

Women

Moderately severe to severe signs of androgenisation, such as hirsutism or acne. Women of childbearing potential should combine cyproterone with ethinyloestradiol to ensure contraception. This also promotes regular menstruation.

Men

Reduction of drive in sexual deviations and inoperable prostatic carcinoma.

The section on contraindications is divided for men and for women like in the Swedish SPC. Liver disease is a contraindication in both groups. Section 4.4, Special warnings and precautions for use, is the same as in the NZ data sheet.

The section about adverse reactions is not divided into effects in men and in women. The most common serious adverse reaction is liver toxicity. It is also stated that in individual cases, disturbances of liver function, some of them severe, have been reported with high-dose Cyprostat treatment. The following adverse reactions affecting the liver are listed in table 3.

Table 3. Adverse reactions affecting the liver.

System organ class (MedDRA)	Very common ≥1/10	Common ≥1/100 and < 1/10	Uncommon ≥1/1000 and < 1/100	Rare ≥1/10000 and < 1/1000	Very rare < 1/10
Hepatobiliary disorders		Hepatic toxicity, including jaundice, hepatitis, hepatic failure*		Increased liver enzymes	Liver function disturbance

* For further information see **PRECAUTIONS**

Under the headline carcinogenicity and mutagenicity, the same information as in the NZ data sheet, section 5.3 is included (11).

Comment: Indications and dosing differ between countries. Information about reactions affecting the liver are rather similar. However, in Sweden the section about adverse reactions is divided between men and women, both including hepatitis but at different frequencies. The Australian PI includes a sentence stating that in individual cases, disturbances of liver function, some of them severe, have been reported with high-dose cyproterone treatment. There is no referral to gender in the text.

2.4 Usage

Usage data for cyproterone is shown in Table 4.

Table 4. Number of cyproterone dispensings from a community pharmacy and number of people receiving a prescription for cyproterone at least once during the year

Year	Cyproterone 50 mg		Cyproterone 100 mg	
	Dispensings	**Nb of people**	**Dispensings**	**Nb of people**
2014	17,253	2,504	1,752	360
2015	17,622	2,458	1,716	374
2016	18,276	2,494	1,691	299
2017	18,897	2,569	1,460	259
2018	19,289	2,837	1,446	265

Source: MoH Pharmaceutical Collection (Data Pharm), extracted 26 March 2019

According to the data base Qlik, using National Collection data for 2018, cyproterone 50 mg was prescribed to 2 836 patients and cyproterone 100 mg was prescribed to 264 patients. The total number of patients prescribed cyproterone was 3 005. Of these, 60% were females and the most common age group prescribed cyproterone was between 20 and 30 years of age.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Bessone F, Lucena MI, Roma MG et al, 2015 (3)

In this Argentinian/Spanish publication, the spectrum of phenotypes and outcomes of cyproterone-induced DILI (drug-induced liver injury) was studied. Twenty-two males (age 70 ± 8 years; range 54–83) developing liver damage as a result of CPA therapy between 1993 and 2013 were included.

Clinical and laboratory data were documented in all cases, liver biopsy findings were reviewed for 7 patients, other causes of hepatitis, such as other medicines or alcohol abuse were ruled out. Duration of therapy with CPA, time to onset of symptoms and clinical features of DILI were investigated. Finally, the clinical and laboratory course of the disease following drug withdrawal was recorded.

Serological markers of viral hepatitis were tested in all patients as well as screening for autoimmune liver disorders and at least one abdominal ultrasound or computed tomography scan. The DILI Severity Index was employed to classify DILI cases as mild, moderate, severe or fatal/transplantation and he Roussel-Uclaf Causality Assessment Method (RUCAM) was used to evaluate causality.

Results

The CPA dose was 150 ± 50 mg/day (range 50–200). Eleven (50%) of the patients were treated with a daily dose of 200 mg. There was no correlation between the daily dose and severity of liver injury. Mean time from initial CPA initial intake to onset of symptoms was 168 ± 97 (range: 33–425) days (all cases except one occurred between 2 and 15 months after initiation of therapy.

Most patients were symptomatic, showing hepatocellular injury (91%) and jaundice. Severity was classified as mild in 1 case (4%), moderate in 7 (32%), severe in 11 (50%) and fatal in 3 (14%). Two patients had cholestatic hepatitis and one patient had a liver injury that resembled autoimmune hepatitis. RUCAM category was 'highly probable' in 19 (86%), 'probable' in 1 (4%), and 'possible' in 2 (9%). Nineteen patients recovered after withdrawal of cyproterone although 3 of them required steroid therapy.

The authors concluded that CPA-induced liver injury is severe, can be fatal and may occasionally resemble autoimmune DILI.

3.1.2 Thole Z, Manso G, Salgueiro E et al, 2004 (12)

This was a review of the literature using MEDLINE and IDIS databases to search for published cases of liver injury induced by antiandrogens (non-steroidal of the flutamide type, or steroidal such as cyproterone). Analysis was made of the type of hepatotoxicity, therapeutic indication, other pharmacological treatment and evolution. Mean values of latency and recovery periods of the adverse reactions and liver function tests were also evaluated.

Results

The search identified 79 published cases of hepatotoxicity suspected of being induced by antiandrogens (72 hepatitis, 6 hepatocellular carcinoma and 1 hepatic cirrhosis). Seven of the cases were women. Hepatitis was associated with all antiandrogens, and in 21 reports the patient had been treated with cyproterone (3 of those patients were women). This adverse reaction did not seem to be dependent on the patients age, therapeutic indication or the dose prescribed. Hepatitis showed a longer latency period for cyproterone acetate than for flutamide. Some transaminase levels were significantly higher for flutamide than for cyproterone acetate, although the evolution was no worse in the cases reported for flutamide. Occasional reports of hepatocellular carcinoma and hepatic cirrhosis suspected of being induced by cyproterone acetate were also found.

The authors note that there are case reports of young women who had been taking low doses of cyproterone or flutamide with or without estradiol and developed hepatitis. They refer to 5 publications, although 4 of these involve flutamide.

3.1.3 Seaman HE, de Vries CS, and Farmer RDT, 2003 (13)

This was a cohort analysis and case-control study in the UK of women aged 15–39 with acne, hirsutism or polycystic ovary syndrome (PCOS) to estimate the risk of liver disorders associated with cyproterone acetate 2 mg combined with ethinyloestradiol 35 µg (CPA/EE).

Results

The researchers identified 172 women who had developed a hepatic event, 25 of the events being hepatitis. In eleven cases the women had been exposed to CPA/EE on the event date, 31 had been exposed to conventional COCs, 126 had not been exposed and 4 had been exposed to other hormonal contraception. Of the eleven cases exposed to CPA/EE, 8 developed altered liver function tests and 3 developed hepatitis.

Compared with cases exposed to conventional combined oral contraceptives (COCs), the age-adjusted incidence rate ratio for liver disorders in women using CPA/EE was 1.7 (95%CI: 0.9,3.4) and compared with no use it was 1.5 (95%CI:0.8, 2.8). The risk of liver disorders in women prescribed CPA/EE was not significantly greater than that in women prescribed conventional COCs (OR: 2.1 [95%CI: 0.9, 4.8]).

The results did not indicate an increased risk for liver disorders associated with CPA/EE use in women with acne, hirsutism or PCOS after adjusting for potential confounding, although the power of the study was low.

Comments: Published data about adverse reactions affecting the liver in women treated with cyproterone is sparse. Most published case reports involve men. In the few reports where the patient is a woman, the treatment has most often been a combination of cyproterone and ethinylestradiol and/or cyclic treatment (although the dosing is not always known). Therefore, it is hard to compare with the CARM case.

However, increased risk of liver disorders does not appear to be a problem with the contraceptive version of cyproterone.

3.2 ADIS Insight

A search in the data base ADIS Insight resulted in 36 reports of cyproterone and liver disorders. The reports came from 19 countries and France was the most frequently reporting country (5 reports). Of the reports, 31 were case reports. The other reports described for example regulatory action or general drug-induced liver injury.

In 8 of the case reports the patients were women. These reports are described below.

1. A 47-year-old woman from the Netherlands developed peliosis hepatis (an uncommon vascular condition characterised by multiple, randomly distributed, blood-filled cavities throughout the liver) following long-term treatment with oral contraceptives which included cyproterone, ethinylestradiol, ethinylestradiol/cyproterone (Diane 35), ethinylestradiol/desogestrel and ethinylestradiol/levonorgestrel. Her history was remarkable for the use of oral contraceptives, for more than 30 years as treatment of acne vulgaris. She had used cyproterone 50 mg both continuously for nine months 30 years ago, and later as cyclical treatment. She stopped using cyproterone in 1995 but continued using other oral contraceptives. At presentation a liver biopsy showed occasional dilated sinusoids suggesting peliosis hepatis. The biopsy was complicated by a sub-capsular liver haematoma. After

discontinuation of oral contraceptives, liver ultrasonography showed regression of the multiple hypervascular lesions.

2. A 22-year-old woman in China developed Budd-Chiari syndrome (occlusion of the hepatic veins that drain the liver) and cholecystitis 7 days after starting treatment with ethinylestradiol/cyproterone 35µg/2mg (1 tablet/day) for irregular menstruation. The route of administration was not stated. The cause was suggested to be related to the use of ethinylestradiol.
3. A Turkish 17-year-old girl developed autoimmune hepatitis 2 months after starting treatment with a combination of ethinylestradiol 2 mg and cyproterone 0.035 mg daily for hirsutism and acne. The treatment was discontinued but her liver enzymes did not return to normal for 2 months. Prednisolone treatment was started, and azathioprine treatment was later added. A liver biopsy taken a year later was consistent with a progressive cirrhotic process although, at last follow-up, she remained clinically well.
4. Hepatocellular carcinoma was identified in a 45-year-old German woman with no history of hepatitis, alcoholism or hepatic cirrhosis. She had received a combination of ethinylestradiol and cyproterone for 14 years [dosages not stated] for contraception. She had also received oral contraceptives of unknown composition for 8 years prior to this.

   The risk of hepatocellular carcinoma in relation to treatment with cyproterone has been discussed over the years. A German study from 1997, where 2,506 patients treated with cyproterone were followed up retrospectively (602 patients for more than 10 years) did not find a connection (14). However, a Japanese report suggested a link between liver cancer and cyproterone therapy in 3 young women (see report 5 below).

   The EMA in 1995 added a warning on packages containing ≥ 50mg cyproterone and in the SmPC for cyproterone under Section 4.4 Warnings and Precautions:

   In very rare cases benign and malignant liver tumours, which may lead to life-threatening intra-abdominal haemorrhage have been observed after the use of Androcur. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be considered in the differential diagnosis.

   This text is also included in the NZ data sheet.
5. Hepatocellular carcinoma developed in 3 women in Japan 9–10 years after they began high-dose cyproterone therapy 100-300 mg/day for 3 to 10 years (15). The author commented that the unusually young age of onset and lack of evidence to suggest chronic hepatitis, suggest that the hepatocellular carcinoma might be associated with cyproterone.
6. Cytolytic and cholestatic jaundice developed in a 24-year-old French woman 3 months after initiating cyproterone therapy for hirsutism. She had received cyproterone (Androcur®) 100 mg/day on day 5-25 and oestradiol (Oestrogel®) 3 mg/day on days 15-25 of the menstrual cycle. Both agents were discontinued, and liver enzymes were normal 6 months later.

3.3 Vigilyze

[redacted]

[redacted]

3.4 Company reports

[redacted]

3.5 CARM data

CARM received 15 case reports of liver related reactions in relation to treatment with cyproterone up to 30 September 2019. In 2 of the reports the patient was female. The details of those 2 reports are summarised below. Details and a summary of all the cases from CARM is attached to this report, see Annexe 2.

Report 131207

[redacted]

[redacted]

Report 029436

[redacted]

4.0 DISCUSSION AND CONCLUSIONS

Cyproterone is a steroid hormone with antiandrogen, progestational and antigonadotrophic effect. Following oral administration, most of the dose is slowly metabolised and excreted mainly in the bile. Accumulation in serum may occur during continuous treatment. The most serious ADRs in patients receiving cyproterone acetate are hepatic toxicity. The NZ data sheet states that cases of direct hepatic toxicity have been reported in patients treated with 200 – 300 mg cyproterone acetate and most reported cases are in men with prostate cancer.

Even if more reactions have been reported in men, cases of hepatic toxicity in women treated with cyproterone have been reported, also in New Zealand. Evidence from the literature regarding liver toxicity associated with cyproterone in women is very limited.

When cyproterone is prescribed for women it may be for cyclical or continuous treatment. Cyproterone is prescribed in combination with ethinylestradiol or as monotherapy and the dosing varies widely depending on indication and other factors such as if the woman is pre- or postmenopausal or if she has had a hysterectomy. It is hard to get information about the dosing from case reports.

According to the data sheet, the risk of liver injury in association with cyproterone is higher with a higher dose. The dose prescribed for men is often much higher than for women. However, some women are prescribed daily cyproterone, for example in the dose 50 mg, where the risk of liver toxicity may be higher compared to cyclic treatment.

The information in the data sheet may be of limited value, both regarding the dose where hepatic reactions occur, and as reactions also occur in women. The product information in some other countries lists hepatic adverse reactions for women, although with unknown frequency. Therefore the Committee may consider that the data sheets could be improved.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The data sheets for cyproterone tablets should be updated regarding the risk of hepatic toxicity.
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. Company reports.
2. CARM data.

7.0 REFERENCES

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