

intracavernosal methylthionium chloride, particularly in patients with drug-induced priapism; it is thought to act by blocking the vasodilator effects of nitric oxide. However, penile necrosis has occurred⁴ after the use of methylthionium chloride and it should probably be avoided in patients with corporal fibrosis; aspiration of methylthionium chloride about 5 minutes after injection has been suggested.^{2,3}

1. Steers WD, Selby JB. Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1991; **146**: 1361-3.
2. deHoll JD, et al. Alternative approaches to the management of priapism. *Int J Impot Res* 1998; **10**: 11-14.
3. Martínez Portillo FJ, et al. Methylene blue as a successful treatment alternative for pharmacologically induced priapism. *Eur Urol* 2001; **39**: 20-3.
4. Hübner J, et al. Methylene blue as a means of treatment for priapism caused by intracavernous injection to combat erectile dysfunction. *Int Urol Nephrol* 2003; **35**: 519-21.
5. Mejean A, et al. Re: Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1993; **149**: 1149.

Preparations

BP 2008: Methylthionium Injection;
USP 31: Methylene Blue Injection.

Proprietary Preparations (details are given in Part 3)

Hung.: Metienkek; **USA:** Urolene Blue.

Multi-ingredient: **Arg.:** Lagrimas de Santa Lucia; Mictasol Azul; Muelita; Visubril; **Austria:** Methymet; **Braz.:** Acridin; Cystex; Lisian; Pilulas De Witts; Sepurin; Vislin; Visodin; Visolux; **Canad.:** Collyre Bleu; **Fr.:** Collyre Bleu; Pastilles Monleon; **Hong Kong:** Clear Blue; **Israel:** Pronest; **Ital.:** Mictasol Bleu; Visustrin; **NZ:** De Witts Pills; **Pol.:** Ginjal; Mibalin; **Rus.:** Neo-Anusol (Нео-анусол); **Spain:** Argentofenol; Centilux; Tivitis; **Switz.:** Collyre Bleu Laiter; **Turk.:** Bucu Bleu; Helmobleu; **USA:** Atrosept; Dolsed; MHP-A; MSP-Blu; Prosed/DS; Trac Tabs 2X; UAA; Urelle; Uret-rion; Uridon Modified; Unimar-T; Unimax; Urised; Uriseptic; UrSym; Uritact; Uro Blue; Urogresic Blue; Utra.

Milk Thistle

Cardo mariano; Chardon marie (milk-thistle fruit); Lady's Thistle; Maarianohdakkeenhedelmä (milk-thistle fruit); Margainiu vaisiai (milk-thistle fruit); Marian Thistle; Mariatistelfrukt (milk-thistle fruit); Mariendistel; Plod ostropestřee mariánského (milk-thistle fruit); Silybi mariani fructus (milk-thistle fruit); St Mary's Thistle. **CAS** — 84604-20-6 (milk thistle extract).

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

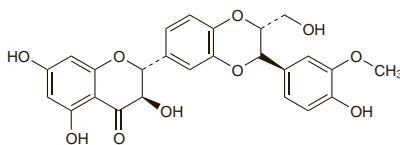
Ph. Eur. 6.2 (Milk-Thistle Fruit). The mature fruit, devoid of the pappus, of *Silybum marianum*. It contains not less than 1.5% of silymarin expressed as silibinin (dried drug). Protect from light. **USP 31** (Milk Thistle). The dried ripe fruit of *Silybum marianum* (Asteraceae), the pappus having been removed. It contains not less than 2% of silymarin, calculated as silibinin, on the dried basis. Store in airtight containers. Protect from light.

Silibinin (rINN)

Silbinina; Silibinine; Silibininum; Silybin; Silybum Substance E₆; Silybinina. 3,5,7-Trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxan-6-yl]-4-chromanone.

Силибинин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 22888-70-6.



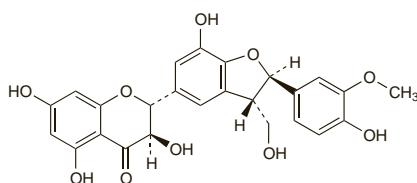
NOTE. The name silymarin has been used for both a mixture of silibinin, silicristin, and silidianin, and for silibinin alone.

Silicristin (rINN)

Silicristina; Silicristine; Silicristinum; Silikrystyna; Silychristin. 2-[2,3-Dihydro-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-5-benzofuran-7-yl]-3,5,7-trihydroxy-4-chromanone.

Силикристин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 33889-69-9.

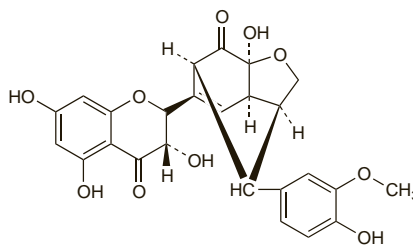


Silidianin (rINN)

Silidianina; Silidianine; Silidianium; Silydianin. (+)-2,3a,3aa,7a-Tetrahydro-7aa-hydroxy-8(R⁺)-(4-hydroxy-3-methoxyphenyl)-4-(3a,5,7-trihydroxy-4-oxo-2β-chroman-1-yl)-3,6-methanobenzo-furan-7(6aH)-one.

Силлидианин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 29782-68-1.



Silymarin

Silimarin; Silymarinum. A mixture of the isomers silibinin, silicristin, and silidianin.

CAS — 65666-07-1.

ATC — A05BA03.

ATC Vet — QA05BA03.

Profile

Milk thistle (*Silybum marianum*; *Cardus marianus*) is used in herbal medicine, mainly for gastrointestinal and hepatobiliary disorders. The fruit contains the active principle silymarin, a mixture of flavonolignans including the isomers silibinin, silicristin, and silidianin, of which silibinin is the major component. Silymarin is claimed to be a free radical scavenger and to have hepatoprotectant properties; it has been used in various liver disorders, as well as to prevent hepatotoxicity associated with poisoning. In *Amanita phalloides* poisoning (p.2349) both silymarin and silibinin (as the disodium dihemisuccinate salt) have been used.

Milk thistle is usually given as a standardised extract containing mainly silymarin, although the herb and fruit have also been used; the strength of the extract is expressed in terms of silymarin or silibinin, although the exact equivalence is not always clear. It is usually given orally since silymarin is poorly water-soluble and therefore unsuitable for intravenous use. A typical oral dose of up to 140 mg of silymarin two or three times daily has been suggested for hepatic disorders. Disodium silibinin dihemisuccinate is water-soluble and is given intravenously; the usual dose in *Amanita phalloides* poisoning is equivalent to silibinin 20 mg/kg daily, given by intravenous infusion in 4 divided doses.

Amanita poisoning. Silymarin and silibinin have been found to be effective in preventing hepatotoxicity after amanita poisoning.^{1,3}

1. Lorenz D. Über die anwendung von silibinin bei der knollenblät-terpilzvergiftung. *Dtsch Arch* 1982; **79**: 43-5.
2. Hruby K, et al. Chemotherapy of *Amanita phalloides* poisoning with intravenous silibinin. *Hum Toxicol* 1983; **2**: 183-90.
3. Enjalbert F, et al. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; **40**: 715-57.

Liver disorders. References to the use of milk thistle or silymarin in patients with liver disorders.

1. Saller R, et al. The use of silymarin in the treatment of liver diseases. *Drugs* 2001; **61**: 2035-63.
2. Jacobs BP, et al. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. *Am J Med* 2002; **113**: 506-15.

Preparations

USP 31: Milk Thistle Capsules; Milk Thistle Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Benevolus; Laragon; **Austral.:** Biogan Liver-Vite; Herbal Liver Formula; Profit; Silymarin Phytosome; **Austria:** Apilhepar; Ardeyhepar; Legalon; Silyhexal; **Belg.:** Legalon; Legalon SIL; **Braz.:** Eleparon; Legalon; Silver; **Chile:** Legalon; **Cz.:** Flavobion; Lagosa; Legalon; Nat Cubetu Benediktu; Silygal; **Fr.:** Legalon; **Ger.:** Alepa; Ardeyhepar; Cefasilymarin; durasilymarin; Hegrimarin; Hepa-Loges; Hepa-Merz Sili; HepaBesch; Hepaduran V; Hepar-Pasc; Heparsy; N; Hepatos; Heplant; Lagosa; Legalon; Legalon SIL; Lomacholan; Phytohepar; Poikicholan; Silbene; Silcur; Silymarin; Silmar; Silyvasan; Sily-Sabona; **Gr.:** Legalon; **Hong Kong:** Legalon; **Hung.:** Hegrimarin; Legalon; Legalon SIL; **India:** Limarin; Silybon; **Ital.:** Legalon; Silmarin; Silirex; Siliver; **Mex.:** Etagem; **Philipp.:** Hepavit; Legalon; Liveraid; **Pol.:** Flexiderm; Lagosa; Legalon; Silimac; Silycaps; Silymarin; Silyverin; **Port.:** Legalon; Legalon SIL; **Rus.:** Carsil (Карсил); **S.Afr.:** Legalon; **Spain:** Legalon; Legalon SIL; Silanine; Silimazul; **Switz.:** Legalon; Legalon SIL; **Thai.:** Legalon; Leveron; Marina; Samarin; Silylar; **Ven.:** Legalon.

Multi-ingredient: **Arg.:** Bibol Leloup; Hepadigenor; Quelodan F; **Austral.:** Antioxidant Forte Tablets; Bupleurum Complex; Bupleurum Compound; Digest; Extralife Liva-Care; Herbal Cleanse; Lifesystem Herbal Formula 7 Liver Tonic; Liver Tonic Herbal Formula 6; Livstim; Livton Complex; Silybum Complex; St Mary's Thistle Plus; **Austria:** Hepabene; **Braz.:** Silamal; **Canad.:** Milk Thistle; Milk Thistle Extract Formula; **Cz.:** Hepabene; Iberogast; Naturland Grosser Swedenbitter; Simepar; Ungolen; **Ger.:** Bilisan Duo; Cheiranthol; Cholhepan N; Cholosom-Tee; Gallexier; Galloselect M; Hepaticum-Medice H; Heumann Leber- und Gallente Solu-Hepar S; Heumann Verdauungstee Solu-Lipar; Heusin; Iberogast; Marianon; Pankreaplex Neu; Pascopankreat novot; Presselin

Hepaticum P; Schwhepan S; Venacton; **Hong Kong:** Hepatofalk Planta; Simepar; **Hung.:** Hepabene; **India:** Livosi-B; **Indon.:** Aptivium Liver Support; Curliv Plus; Hepa-Q; Hepamax; Heparviton; Hepasil; Hepatin; Hepatofalk Planta; Verona; Vionin NF; **Ital.:** Depatox; Epagast; Liverton; Tarassaco (Specia Composta); Venoplus; **Malaysia:** Hepavit; Simepar; **Philipp.:** Liverine; Livermin; **Pol.:** Artecholol; Artecholox; Gastrobonisol; Silycinar; Silyvit; Tabletki Przeciw Niestrawnosci; **Port.:** Cholagut; Synchrorose; **Rus.:** Hepabene (Гепабене); Silbectan (Силбектан); **Singapore:** Hepatofalk Planta; Hepavit; Nonicaven; Simepar; **Switz.:** Demonatur Gouttes pour le foie et la bile; Iberogast; Phytomed Hepato; Simepar; Tisane hepatiche et biliaire.

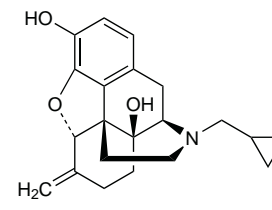
Nalmefene (BAN, USAN, rINN)

6-Desoxy-6-methylene-naltrexone; JF-1; Nalmefène; Nalmefeno; Nalmefenum; Nalmetrene; ORF-11676. 17-(Cyclopropylmethyl)-4,5a-epoxy-6-methylenemorphinan-3,14-diol.

Налмифен

$C_{21}H_{25}NO_3$ = 339.4.

CAS — 55096-26-9.



Nalmefene Hydrochloride (BANM, rINN)

Hydrocloruro de nalmefeno; Nalmefène, Chlorhydrate de; Nalmefeni Hydrochloridum; Nalmetrene Hydrochloride.

Налмифена Гидрохлорид

$C_{21}H_{25}NO_3 \cdot HCl$ = 375.9.

CAS — 58895-64-0.

Adverse Effects

Nausea, vomiting, tachycardia, hypertension, fever, and dizziness have been reported with therapeutic doses of nalmefene. At higher doses or in patients later found to be physically dependent on opioids, symptoms suggestive of opioid withdrawal have been noted; these have included abdominal cramps, chills, dysphoria, myalgia, and joint pain.

Precautions

As for Naloxone, p.1453.

Incremental doses of nalmefene should be given slowly in patients with renal impairment.

Pharmacokinetics

Nalmefene is absorbed after oral doses but bioavailability is not complete owing to significant first-pass metabolism. It is metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine. Some of the dose is excreted in the faeces and it may undergo enterohepatic recycling. The plasma elimination half-life is reported to be about 10 hours.

References

1. Dixon R, et al. Nalmefene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986; **39**: 49-53.
2. Dixon R, et al. Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. *J Clin Pharmacol* 1987; **27**: 233-9.
3. Frye RF, et al. The effect of age on the pharmacokinetics of the opioid antagonist nalmefene. *Br J Clin Pharmacol* 1996; **42**: 301-6.
4. Frye RF, et al. Effects of liver disease on the disposition of the opioid antagonist nalmefene. *Clin Pharmacol Ther* 1997; **61**: 15-23.

Uses and Administration

Nalmefene is a derivative of naltrexone and is a specific opioid antagonist with actions and uses similar to those of naloxone (p.1454), but with a longer duration of action. It is given as the hydrochloride but doses are expressed in terms of the base. Nalmefene hydrochloride 111 micrograms is equivalent to about 100 micrograms of nalmefene. It is usually given intravenously for a rapid onset of action; subcutaneous or intramuscular administration is also effective but has a slower onset. Nalmefene has also been given orally.

For the reversal of postoperative central depression due to the use of opioids, nalmefene is given intravenously,