

Management of the woman with threatened birth of an infant of extremely low gestational age

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Objective: To offer guidelines for parents, physicians and other members of the health-care team for management of the probable birth of an infant with a gestational age of 26 completed weeks or less.

Options: Vaginal birth or birth by cesarean section for fetal indications and active treatment or palliative care of the infant at birth.

Outcomes: Increased risk of complications for the mother from cesarean section at this stage of pregnancy and the difficulty in making a prognosis before or at birth for an infant of this gestational age.

Evidence: Published survival rates and risks of impairment or disability for infants of each gestational age; current information provided by directors of follow-up clinics in Canadian university-based pediatric programs.

Values: The recommended management of the woman and her fetus or infant is based on many underlying considerations, including the best interests of the mother and her infant and the views of fully informed parents.

Benefits, harms and costs: Use of these guidelines will enable health care providers to offer parents of infants of extremely low gestational age therapeutic choices before birth based on full information on likely outcomes, to avoid unnecessary cesarean section and to minimize suffering when treatment of infants is not in their best interests.

Recommendations: According to current Canadian outcome data, fetuses with a gestational age of less than 22 completed weeks are not viable and those with an age of 22 weeks rarely viable. Their mothers are not, therefore, candidates for cesarean section, and the newborns should be provided with compassionate care, rather than active treatment. The outcomes for infants with a gestational age of 23 to 24 completed weeks vary greatly. Careful consideration should be given to the limited benefits for the infant and potential harms of cesarean section, as well as to the expected results of resuscitation at birth. Cesarean section, when indicated, and any required neonatal treatment are recommended for infants with gestational ages of 25 and 26 completed weeks; most infants of this age will survive, and most survivors will not be severely disabled. Treatment of all infants with a gestational age of 22 to

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26 weeks should be tailored to the infant and family and should involve fully informed parents.

Validation: Members of the Fetus and Newborn Committee of the Canadian Paediatric Society (CPS) were involved in the preparation of this article, which was reviewed and modified by the Ethics Committee of the CPS and the Maternal-Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC). A draft was circulated to Canadian university-based perinatal programs and members of the Section on Neonatal-Perinatal Medicine of the CPS. Comments from physicians and bioethicists were incorporated, when possible, into the final version. There are no similar guidelines in North America.

Sponsors: These guidelines were sponsored and endorsed by the CPS and the SOGC.

Objectif : Offrir aux parents, aux médecins et aux autres membres de l'équipe de soins des lignes directrices sur la gestion de la naissance probable d'un nouveau-né à 26 semaines complètes ou moins de gestation.

Options : Accouchement par voie vaginale ou césarienne en cas de signes foetaux et traitement actif ou administration de soins palliatifs au nouveau-né à la naissance.

Résultats : Risque accru de complications pour la mère à la suite d'une césarienne à ce stade de la grossesse et pronostic difficile avant la naissance, ou au moment de celle-ci, d'un nouveau-né à ce stade de la gestation.

Preuves : Taux de survie publiés et risques d'incapacité ou de déficience chez les nouveau-nés des divers stades de gestation; renseignements courants fournis par les directeurs de cliniques de suivi dans des programmes universitaires de pédiatrie au Canada.

Valeurs : Le traitement recommandé de la mère et du fœtus ou du nouveau-né est fondé sur de nombreuses considérations sous-jacentes, y compris le meilleur intérêt de la mère et de son nouveau-né et les vues des parents pleinement informés.

Avantages, préjudices et coûts : Ce guide de pratique permettra aux fournisseurs de soins de santé d'offrir aux parents de nouveau-nés dont l'âge gestationnel est extrêmement bas des choix thérapeutiques avant la naissance, qui seront fondés sur des renseignements complets relatifs aux résultats probables, afin d'éviter des césariennes inutiles et de réduire au minimum les souffrances lorsque le traitement des nouveau-nés n'est pas dans leur meilleur intérêt.

Recommandations : D'après les données courantes sur les résultats au Canada, à moins de 22 semaines complètes de gestation, un fœtus n'est pas viable et il l'est rarement à 22 semaines. La mère n'est donc pas candidate à une césarienne et le nouveau-né devrait être l'objet d'interventions de soulagement au lieu de recevoir des traitements. Dans le cas des nouveau-nés qui ont de 23 à 24 semaines complètes de gestation, les résultats varient énormément. Il faudrait analyser attentivement les avantages limités pour l'enfant et les dangers possibles de la césarienne, ainsi que les résultats attendus de la réanimation à la naissance. Lorsqu'elle est indiquée, la césarienne et tout traitement néonatal requis sont recommandés pour les nouveau-nés qui ont 25 et 26 semaines complètes de gestation. La plupart des nouveau-nés de cet âge survivront et la plupart des survivants n'auront pas de handicap grave. Le traitement de tous les nouveau-nés qui ont de 22 à 26 semaines de gestation devrait être personnalisé selon le nouveau-né et la famille, et les parents devraient être bien informés et avoir leur mot à dire.

Validation : Des membres du Comité d'étude du fœtus et du nouveau-né de la Société canadienne de pédiatrie (SCP) ont participé à la rédaction de cet article, qui a été critiqué et modifié par le Comité d'éthique de la SCP et le Comité de médecine foeto-maternelle de la Société des obstétriciens et gynécologues du Canada (SOGC). Une version préliminaire a été distribuée aux programmes périnataux universitaires du Canada et aux membres de la Section de la médecine néonatale et périnatale de la SCP. On a intégré dans la mesure du possible les commentaires de médecins et de bioéthiciens dans la version finale. Il n'existe aucun guide de pratique semblable en Amérique du Nord.

Commanditaires : Ces lignes directrices ont été parrainées et appuyées par la SCP et la SOGC.

This article offers guidance to parents, physicians and other members of the health care team facing the probable birth of an infant of extremely low gestational age: 22 to 26 completed weeks. Although the prevalence of such births is very low, slightly less than 2 per 1000 births,¹ the effect on the infant and parents is

profound. Recent advances in treatment have increased survival rates for infants born at this stage of gestation. In addition, the death rate decreases rapidly with each week of gestation.²⁻⁵ A recent decrease in the prevalence of impairment and disabilities in surviving infants has also been reported;⁶⁻¹⁰ however, the rate of reduction has

lagged behind that of the mortality rate. Consequently, the number of infants with impairments or disabilities may be increased, but the increase in the number of neurologically intact survivors is even greater.

Early-gestation birth is attended by extraordinarily complex and difficult ethical decisions. All of the ethical principles come into play in determining what is best for the mother and her infant. At 22 weeks' gestation, autonomy of the mother and physician nonmaleficence and beneficence toward her are paramount considerations in treatment decisions. As pregnancy progresses, concern for the life and health of the fetus or infant rapidly increases. Distributive justice considerations may complicate the physician's concern for an infant and family: although there are few infants of extremely low gestational age, care of these infants requires very great use of the resources of a neonatal intensive care unit (NICU), and resource use escalates rapidly the lower the gestational age.^{11,12} Hence, physicians' concerns are complicated by pressures to distribute equitably the limited health care resources.

In the following discussion we use the definition of gestational age in the *International Classification of Disease* (ICD-10).¹³ For clarity, gestational age is expressed in completed days and weeks. For example, the period 22 weeks and 0 days to 22 weeks and 6 days (154 days to 160 days inclusive) of gestation is referred to as "22 completed weeks."

The birth of a child of a gestational age of 22 to 26 completed weeks is fraught with uncertainty concerning the chance of survival and the risk of impairment and disability. Although survival and disability rates are of some help, it is often impossible to make a prognosis before birth. Accurate prognosis, especially of long-term outcome, is almost as difficult in the first few days after birth. This uncertainty may cause extreme stress for parents and caregivers around the time of the birth and during the neonatal period. Moreover, despite the use of pain control, the pain and suffering experienced by the infant in intensive care cannot be determined.

Twins and other multiple fetuses are overrepresented in early-gestation birth; they face higher disability and death rates than singletons of a comparable gestational age.¹⁴ The number of multiple births has increased in recent years because of in-vitro fertilization and hormonal stimulation of ovulation.

Because gestational age is sometimes unknown or inaccurate, most data on deaths and disabilities in early-gestation infants are given by birth weight. However, other than an estimate from ultrasonographic examination, fetal weight is unavailable to obstetricians and neonatologists before birth. Therefore, our guidelines for management are based on gestational age in completed weeks, although we recognize that this may be inaccurate. The guidelines provide a way to balance ethical considerations concerning, on the one hand, the short-term and long-term risks of death and disability in fetuses and infants and, on the other, the emotional and

physical burdens such premature births place on parents. We also give some guidance to physicians confronted with the difficult decision to start or withhold treatment of such infants at birth. This article does not address later management in the NICU. Such management should be guided by an earlier statement by the Canadian Paediatric Society.¹⁵

Methods

Drafts of these guidelines were distributed to staff of all Canadian university tertiary perinatal centres, members of the Section on Neonatal-Perinatal Medicine of the Canadian Paediatric Society, several bioethicists and other physicians, who reviewed them and provided input. Practice in this difficult area of perinatal care varies; these guidelines were written with these differences in mind. We emphasize the need for joint decision making with fully informed parents. These guidelines have been approved by the Canadian Paediatric Society and the Society of Obstetricians and Gynaecologists of Canada.

Principles of management

The preferred management of a woman with a threatened birth of an infant of this gestational age is consultation with a perinatologist in a tertiary care centre followed, if appropriate, by admission to the centre.

Ideally, the management of a woman at risk of giving birth at this stage of pregnancy should be multidisciplinary and unified. The skills and knowledge of specialists in maternal-fetal medicine and neonatology should be combined and complemented by the expertise and involvement of nurses, social workers and other professionals.

The best available assessment of fetal health status, gestational age and weight, and information concerning the short-term and long-term risks and benefits of outcomes for the mother, fetus and infant are needed to make recommendations for management.

The following information should be given to the parents and should form the basis of such recommendations:

- immediate risks to the mother of continuation of the pregnancy;
- immediate and long-term risks to the mother of different methods of delivery, especially the risk for future pregnancies posed by classic cesarean section; and
- short-term and long-term outcomes for fetuses and infants at the perinatal centre involved, by fetal weight, gestational age and number of fetuses.

Plans for management should be based on reasonable expectations and should respect the wishes of the parents, the best interests of the infant and the recommendations of the health care team. If the parents and health care team do not agree, differences can usually be resolved through further discussion with other profes-

sionals (e.g., the hospital ethics committee), if necessary and as time allows.

Planned collaborative decision making may be limited as the result of an unanticipated premature birth or a serious illness in the mother or fetus.

Management plans discussed with parents should be flexible in regard to starting, withholding or withdrawing treatment; these plans may need to be changed at birth or afterward, depending on the status of the infant.

A neonatologist or delegate should attend births of infants of this gestational age to help with treatment decisions based on the condition of the infant.

Whenever possible, a decision to withhold or withdraw treatment immediately after birth should be made jointly, through full discussion, by the physician, the parents and appropriate members of the health care team. Decisions should be clearly documented in the medical record.

In all cases the infant should be given compassionate care, including warmth and pain relief required for comfort.

Programs for the management of births of infants of an extremely low gestational age should include suitable clinical audits of perinatal death and disability, including the long-term outcome for surviving infants. In addition, such programs should hold regular courses in conjunction with hospitals in their catchment areas to inform staff of advances in care.

Determination of gestational age and fetal weight

Menstrual history, corroborated by the results of an ultrasonographic examination, provides the best estimate of gestational age.¹⁶ Complete antenatal records, including the results of a first-trimester pelvic examination, previous ultrasonographic examinations and measurements of symphysis-fundus height, should be consulted.

If gestational age is unknown, it can be estimated adequately from the results of ultrasonographic examinations. Prediction of gestational age from ultrasonography is reported to be accurate to within 8 days in the first trimester and 20 days in the second trimester.¹⁷

An ultrasonographic examination to determine the biometric and morphologic features and weight of the fetus should precede discussions concerning the management of the birth if time permits. Estimates of fetal weight obtained from ultrasonographic examinations vary within 10% to 15% of the true weight, depending on the amount of amniotic fluid, fetal presentation and lie, biometric indices used to calculate weight and the expertise of the estimator.¹⁸ Table 1 gives approximate mean birth weights for infants with gestational ages from 22 to 26 completed weeks.¹³

As part of the ultrasonographic examination for fetal biometry, clinicians should make a careful search for congenital anomalies. Any maternal or fetal risk factors

for growth restriction should be considered in interpreting an estimate of fetal weight.

Guidelines for management

Many physicians have requested information and guidance about referring woman with a threatened birth of an early-gestation infant and about starting or withholding treatment of infants of specific gestational ages. Such guidance must be general because data on outcomes are changing; in any particular centre outcomes will be influenced by numerous factors. Moreover, although parents may insist on treatment when first confronted with the likelihood of a very premature birth, they may hold less definite opinions after they understand the implications of a birth at the extreme limits of viability.

These guidelines summarize practices in Canadian perinatal centres and outcomes from these centres. Published outcome data have been supplemented with unpublished information obtained from the directors of follow-up clinics in seven Canadian university-based tertiary care programs (Drs. Edmond Kelly, Mount Sinai Hospital, Toronto, Ont.; Marie Kim, St. Joseph's Health Centre, London, Ont.; Charlene Robertson, Royal Alexandra Hospital, Edmonton, Alta.; Saroj Saigal, Chedoke-McMaster Hospitals, Hamilton, Ont.; Reginald Sauve, Foothills Hospital, Calgary, Alta.; Michael Vincer, Grace Maternity Hospital, Halifax, NS; and Michael Whitfield, British Columbia's Children's Hospital, Vancouver, BC: unpublished data, 1993).

Parents should be informed that the statistics provided to them by the centre are retrospective and based on small numbers; however, they are the best evidence available. As we noted earlier, whenever possible the data on outcomes should be specific to the perinatal centre. As well, parents need to be informed that the treatment offered by the perinatal team is tailored to their needs and the needs of their infant.

Infants with a gestational age of less than 22 completed weeks (154 days)

Treatment decisions should be based on the health of the mother. At this stage of gestation the fetus is not

Table 1: Approximate mean birth weights of infants with a gestational age of 22 to 26 completed weeks

Gestational age (completed weeks)	Birth weight (grams)
22	500
23	600
24	700
25	800
26	900

viable; therefore, cesarean section provides no benefit to the fetus and should be performed only if indicated for the mother's health.

Since infants of this gestational age cannot be expected to survive, they should be given only compassionate palliative care. However, the neonatologist may decide to provide active treatment for apparently viable infants whose gestational age may have been underestimated.

Infants with a gestational age of 22 completed weeks (154 to 160 days)

Although very infrequent, the survival of such infants is reported; it depends partly on individual variations in physiologic maturity. Accounts of survival at this gestational age are mainly anecdotal, and so data on disability in survivors are limited.

Treatment decisions should be based primarily on the health of the mother. Because the mother would be subjected to unjustifiable risk, cesarean section should not be performed except when it is indicated for the mother's health. Women requesting cesarean section for an infant of this gestational age should, if at all possible, be dissuaded.

Because so few infants born at this gestational age are expected to live, most can be offered only compassionate palliative care. Active treatment should be started only at the request of fully informed parents or if it appears that the gestational age has been underestimated.

Infants with a gestational age of 23 to 24 completed weeks (161 to 174 days)

Infants born at just 23 weeks may have very different prognoses from those born at almost 25 weeks. Reported neonatal survival rates increase rapidly within this 2-week interval, varying from 10% to 50%.^{2-5,19-21}

Among surviving infants 20% to 35% have disabilities such as cerebral palsy, hydrocephalus, severe cognitive deficit, blindness, or deafness, or a combination of these.^{6,9-11} Although most disabilities²² in these infants are mild or moderately severe,^{6,9} up to 10% are severe and necessitate significant caretaking, far beyond that usually required by infants of their age.⁹

In cases of fetal distress cesarean section is rarely performed, owing to the high rates of infant mortality and to the risk of adverse outcomes in subsequent pregnancies resulting from the types of uterine incision used. Exceptions are more appropriate in infants with gestational ages approaching 25 weeks. Informed parents may wish to override the obstetrician's opinion that a cesarean section should not be performed. In such cases, a second consultation may be obtained and care of the mother transferred to a colleague without prejudice.

The initial management of an infant of this age

should be consistent with the parents' wishes. For most of such infants without fatal congenital anomalies management may include resuscitation. However, clinicians should discuss with the parents the need for flexibility in deciding to start or withhold resuscitation, depending on the infant's condition at birth.

Infants with a gestational age of 25 to 26 completed weeks (175 to 188 days)

Survival rates for infants of this gestational age are currently 50% to 80%.^{2,3,5,20,21} Impairments and disabilities²² such as those previously described affect 10% to 25% of these infants.^{6,9}

Decisions concerning the mode of delivery should be based on the best interests of the mother and infant. Cesarean section is the accepted mode if the fetus is compromised during labour. If the parents initially refuse a cesarean section the clinician must confirm that the parents fully understand the implications and likely outcomes of their decision.

In addition, resuscitation should be attempted for all infants of this gestational age without fatal anomalies.

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References

1. *Births and Deaths* (Vital Statistics ser, vol 1, cat no 84-204), Statistics Canada, Ottawa, 1985
2. Phelps DL, Brown DR, Tung B et al: 28-day survival rates of 6676 neonates with birthweights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17
3. Hack M, Horbar JD, Malloy MH et al: Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics* 1991; 87: 587-597
4. Liechty EA, Donovan E, Purohit D et al: Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome. *Pediatrics* 1991; 88: 19-28
5. Effer SB, Lopes LM, Whitfield MF: When does outcome justify heroic interventions? Univariate analysis of gestation age-specific neonatal mortality and morbidity. *J Soc Obstet Gynecol Can* 1992; 14 (6): 39-49
6. Saigal S, Rosenbaum P, Hattersley B et al: Decreased disability rates among 3-year-old survivors weighing 501 to 1000 grams at birth and born to residents of a geographically defined region from 1981 to 1984 compared with 1977 to 1980. *J Pediatr* 1989; 114: 839-846
7. Saigal S, Szatmari P, Rosenbaum P et al: Intellectual and functional status at school entry of children who weighed 1000 grams or less at birth: a regional perspective of birth in the 1980s. *J Pediatr* 1990; 116: 409-416

8. Collin MF, Halsey CL, Anderson CL: Emerging developmental sequelae in the "normal" extremely low birth weight infant. *Pediatrics* 1991; 88: 115-120
9. Robertson CM, Hrynchyshyn GJ, Etches PC et al: Population-based study of the incidence, complexity and severity of neurologic disability among survivors weighing 500 through 1250 grams at birth: a comparison of two birth cohorts. *Pediatrics* 1992; 90: 750-755
10. Sauve RS, Guyn LH: Improving morbidity rates in < 750 g infants. [abstract] *Pediatr Res* 1992; 31: 259A
11. *Neonatal Intensive Care for Low Birthweight Infants: Costs and Effectiveness, Health Technology Case Study 38*, US Congress Office of Technology Assessment, Washington, 1987
12. Doyle LW, Murton LJ, Kitchen WH: Increasing the survival of extremely-immature (24-to-28-weeks' gestation) infants — At what cost? *Med J Aust* 1989; 150: 558-568
13. *International Classification of Disease, 10th rev*, vol 1, World Health Organization, Geneva, 1992
14. Hoffman EL, Bennett FC: Birth weight less than 800 grams: changing outcomes and influences of gender and gestation number. *Pediatrics* 1990; 86: 27-34
15. Bioethics Committee, Canadian Paediatric Society: Treatment decisions for infants and children. *Can Med Assoc J* 1986; 135: 447-448
16. Cunningham FG, MacDonald PC, Levine KJ et al (eds): *Williams' Obstetrics*, 19th ed, Appleton and Lange, East Norwalk, Conn, 1993: 853
17. Sabbagha RE (ed): Gestational age. In *Diagnostic Ultrasound Applied to Obstetrics and Gynaecology*, 2nd ed, Lippincott, Philadelphia, 1987: 91-111
18. Mills MD, Nageotte MP, Elliott JP et al: Reliability of ultrasonographic formula in the prediction of fetal weight and survival of very-low-birth-weight infants. *Am J Obstet Gynecol* 1990; 163: 1568-1574
19. Hack M, Fanaroff AA: Outcomes of extremely-low-birth-weight infants between 1982 and 1988. *N Engl J Med* 1989; 321: 1642-1647
20. Ferrara TB, Hoekstra RE, Couser RJ et al: Survival and follow-up of infants 23-26 weeks gestation: effects of surfactant use in a tertiary centre. [abstract] *Pediatr Res* 1992; 31: 247A
21. Mendoza J, Campbell MK, Chance GW: Mortality trends in < 800 gram infants before and after surfactant availability. [abstract] *Pediatr Res* 1992; 31: 255A
22. *International Classification of Impairments, Disabilities and Handicaps: a Manual of Classification Relating to the Consequences of Disease*, World Health Organization, Geneva, 1980

has been cured or has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

Recommended Adult Dosages

Loading Dose: Administration of a loading dose on the first day of treatment, consisting of twice the usual daily dose, results in plasma concentrations close to steady state by the second day. Patients with acute infections should be given a loading dose equal to twice the daily dose, not to exceed a maximum single dose of 400 mg, on the first day of treatment.

Oropharyngeal Candidiasis: 100 mg once daily. Treatment should be continued for at least 2 weeks to decrease the likelihood of relapse.

Esophageal Candidiasis: 100 mg to 200 mg once daily. Patients should be treated for a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms.

Systemic Candidiasis: 200 mg to 400 mg once daily. These patients should be treated for a minimum of 4 weeks and for at least 2 weeks following resolution of symptoms.

Cryptococcal Meningitis: 200 mg to 400 mg once daily. Although the duration of therapy for cryptococcal meningitis is unknown, it is recommended that the initial therapy should last a minimum of 10 weeks.

Prevention of Recurrence of Cryptococcal Meningitis in AIDS: 200 mg once daily.

DIFLUCAN (fluconazole) may be administered either orally or by intravenous infusion. The intravenous infusion of DIFLUCAN should be administered at a maximum rate of approximately 200 mg/hour given as a continuous infusion. See **Directions for Use**.

Dosage in Patients With Impaired Renal Function

Fluconazole is cleared primarily by renal excretion as unchanged drug. In patients with impaired renal function, an initial loading dose of 50 to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine Clearance (mL/min)	Percent of Recommended Dose
>50	100%
21-50	50%
11-20	25%
Patients receiving regular hemodialysis	one recommended dose after each dialysis

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance.

Males:	$\text{Weight (kg)} \times (140 - \text{age})$ $72 \times \text{serum creatinine (mg/100 mL)}$
Females:	0.85 x above value

Composition: DIFLUCAN Tablets (pink) contain 50, 100 or 200 mg fluconazole. Also contains the following non-medicinal ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone, croscarmellose sodium, FD & C Red No. 40 aluminum lake dye, and magnesium stearate.

DIFLUCAN I.V. for infusion is a sterile solution of fluconazole in saline at a concentration of 2 mg/mL which is made iso-osmotic with sodium chloride 9 mg/mL.

Directions for Use: Inspect visually for particulate matter or discoloration prior to administration. Do not use if cloudiness or precipitation is evident.

Reject the contents as unsterile if the metal seal is broken. NOT INTENDED FOR MULTIDOSE USE: discard any portion not used when the seal is first broken.

Connect an intravenous giving set to the bottle of DIFLUCAN (fluconazole) intravenous solution and also insert a venting set through the bung. Infuse DIFLUCAN intravenous solution at a maximum rate of 200 mg/hour. Flush DIFLUCAN intravenous solution remaining in the giving set with sterile normal saline.

Because fluconazole is available as a dilute saline solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

Incompatibility: It is recommended that DIFLUCAN I.V. be infused separately.

Compatibility: Administration sets ("giving" sets).

DIFLUCAN I.V. infusion is compatible with (i.e. not susceptible to absorption) sets constructed of a delivery tube (PVC) luer lock (modified phenylene oxide), flash ball (latex) drip chamber (polypropylene) and piercing spike (polypropylene).

DOSAGE FORMS

Availability: DIFLUCAN TABLETS are available as pink tablets containing 50 mg, 100 mg, and 200 mg of fluconazole.

Supplied in bottles (opaque polyethylene) of 50 or 100 tablets.

DIFLUCAN I.V. is available as a sterile aqueous solution for direct infusion. Each mL contains 2 mg fluconazole and 9 mg sodium chloride. Supplied in clear glass bottles of 100 mL and 200 mL, affording doses of 200 mg and 400 mg fluconazole respectively, sealed with a rubber bung.

STORAGE

DIFLUCAN TABLETS (fluconazole) 50, 100, and 200 mg: Store below 30°C.

DIFLUCAN I.V. (fluconazole) 2 mg/mL: Store below 30°C. Do not freeze.

References: 1. Diflucan® Product Monograph. Data on file. Pfizer Canada Inc. 2. De Repentigny L. Advances in the treatment of fungal infections. Bulletin de Nouvelles CACMID Newsletter. Winter 1992. 3. Compendium of Pharmaceuticals and Specialties. 26th ed. Ottawa, Canada: Canadian Pharmaceutical Association; 1991:492, 802-803. 4. Diflucan® New Drug Submission Studies 155, 171, 349, 351. Data on file. Pfizer Canada Inc. 5. Meunier F, Gerain J, Snoeck R, Libotte F, Lambert C, Ceuppens AM. Fluconazole therapy of oropharyngeal candidiasis in cancer patients. In: Fromtling RA, ed. *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents*. JR Prous Science Publishers; 1987:169-174. 6. Dupont B, Drouhet E. Fluconazole in the management of oropharyngeal candidiasis in a predominantly HIV antibody-positive group of patients. In: Fromtling RA, ed. *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents*. JR Prous Science Publishers; 1987:163-168. 7. De Wit S, Goossens H, Weerts D, Clumeck N. Comparison of fluconazole and ketoconazole for oropharyngeal candidiasis in AIDS. *Lancet*. 1989;1(86):746-748.



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