INDOMETHACIN AGILA
*Indomethacin sodium trihydrate Powder for Injection 1 mg*

**Description**

Indomethacin Agila (indomethacin sodium trihydrate (also known as indometacin sodium trihydrate)) for intravenous administration is lyophilised indomethacin sodium trihydrate.

Indomethacin sodium trihydrate is designated chemically as 1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-, sodium salt, trihydrate.

Its molecular weight is 433.82 g/mol.

Its molecular formula is C$_{19}$H$_{15}$ClNNaO$_{4}$·3H$_{2}$O and

Its structural formula is:

![structural formula of indomethacin](image)

CAS Number: 74252-25-8

Each vial contains indomethacin sodium trihydrate equivalent to 1 mg indomethacin as a sterile white to yellow lyophilised powder or plug. Variations in the size of the lyophilised plug and the intensity of colour have no relationship to the quality or amount of indomethacin present in the vial.

pKa value for Indomethacin is 4.5.

Indomethacin Agila contains no other excipients.

**Pharmacology**

Indomethacin is a non-steroidal anti-inflammatory agent which inhibits prostaglandin synthesis. Although the exact mechanism of action through which indomethacin causes closure of a patent ductus arteriosus is not known, it is believed to be through inhibition of prostaglandin synthesis. Indomethacin has been shown to be a potent inhibitor of prostaglandin synthesis, both *in vitro* and *in vivo*. In human newborns with certain congenital heart malformations, PGE 1 dilates the ductus arteriosus. In fetal and newborn lambs, E type prostaglandins have also been shown to maintain the patency of the ductus, and as in human newborns, indomethacin causes its constriction.

Studies in premature infants with patent ductus arteriosus indicated that, after the first dose of intravenous indomethacin, there was a transient reduction in cerebral blood flow velocity and cerebral blood flow. Similar decreases in mesenteric blood flow and velocity have been observed. The clinical significance of these effects has not been established.
Pharmacokinetics

Absorption: The disposition of indomethacin following intravenous administration (0.2 mg/kg) in pre-term neonates with patent ductus arteriosus has not been extensively evaluated. Even though the plasma half-life of indomethacin was variable among premature infants, it was shown to vary inversely with postnatal age and weight. In one study of 28 evaluated infants, the plasma half-life in those infants less than 7 days old averaged 20 hours (range: 3-60 hours, n=18). In infants older than 7 days, the mean plasma half-life was 12 hours (range: 4-38 hours, n=10). Grouping the infants by weight, the mean plasma half-life in those weighing less than 1000 g was 21 hours (range: 9-60 hours, n=10) and in those infants weighing more than 1000 g, was 15 hours (range: 3-52 hours, n=18).

Distribution: In adults, about 99 percent of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. The percent bound in neonates has not been studied. In controlled trials in premature infants, however, no evidence of bilirubin displacement has been observed as evidenced by an increased incidence of bilirubin encephalopathy (kernicterus).

Excretion: Following intravenous administration in adults, indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean plasma half-life of indomethacin is estimated to be about 4.5 hours. In the absence of enterohepatic circulation, it is 90 minutes.

Clinical Trials

Systematic Reviews Comparing Different Dosing Schedules of Indomethacin for Symptomatic PDA

To date three systematic reviews on indomethacin in symptomatic PDA have been performed comparing:

1. Intermittent prolonged courses (6-8 doses) to intermittent short courses (2-3 doses) [Herrera, Cochrane Database of Systematic Reviews 2007, Issue 2]
2. Continuous infusion (36 hrs) to intermittent bolus injection (3 doses) [Görk, Cochrane Database of Systematic Reviews 2008, Issue 1]
3. Intermittent slow infusion (3 doses, 1-2 courses) to intermittent bolus injection (3 doses, 1-2 courses) [Merck Sharp & Dohme, 2008]

The following table summarises the key selection criteria and findings for each of these reviews:

Table 1

<table>
<thead>
<tr>
<th>Objectives &amp; Inclusion Criteria</th>
<th>Treatments, Studies &amp; Patients</th>
<th>Primary Results by Endpoint</th>
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<tr>
<td>To determine the effect of a prolonged course of indomethacin (compared to a short course) on the rate of treatment failure without unwanted side-effects in preterm infants with PDA. Randomised or quasi-randomised controlled trials including preterm infants with PDA, diagnosed on clinical and/or echocardiographic examination that evaluated indomethacin treatment.</td>
<td>Treatment by any route given as a long course (four or more doses) vs. a short course (three or fewer doses). Five RCTs/quasi RCTs met inclusion criteria and included 431 infants. PDA closure was only reported in 4 trials (361 infants).</td>
<td>To compare intermittent prolonged courses to short courses (Relative Risk [RR], Risk Difference [RD], Number Needed to Treat [NNT] were reported). No significant difference in failure of PDA closure [typical RR 0.82 (95% CI 0.51, 1.33); typical RD - 0.03 (95% CI -0.11, 0.04)]. The prolonged course was associated with an increased risk of NEC [typical RR 1.87 (95% CI 1.07, 3.27), typical RD 0.08 (95% CI 0.01, 0.15); NNT 13 (7, 100)] decreased incidence of renal function impairment, as evidenced.</td>
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by a lower proportion of infants having diminished urine output [typical RR 0.27 (95% CI 0.13, 0.6); typical RD -0.19 (95% CI -0.28, -0.09); NNT 5 (4, 11)] and increased serum creatinine level [typical RR 0.51 (95% CI 0.33, 0.77); typical RD -0.14 (95% CI -0.23, -0.06); NNT 7 (4, 16)].

RR>1 favours short course IV indomethacin.

**Authors’ conclusions - Implications for practice**

Prolonged indomethacin course does not appear to have a significant effect on improving important outcomes, such as PDA treatment failure, CLD, IVH, or mortality. The reduction of transient renal impairment does not outweigh the increased risk of NEC associated with the prolonged course. Based on these results, the author cannot recommend a prolonged course of indomethacin for the routine treatment of PDA in preterm infants.

<table>
<thead>
<tr>
<th>Görk 2008</th>
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<th>Objectives &amp; Inclusion Criteria</th>
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<td>To compare the efficacy and safety of continuous infusion vs. bolus administration of indomethacin in closing a symptomatic PDA in preterm infants. Review included randomised and quasi-randomised controlled trials comparing continuous indomethacin infusion to bolus doses for closure of a symptomatic PDA in preterm infants with a symptomatic PDA diagnosed clinically and/or by echocardiography.</td>
<td>Experimental group: Continuous infusion of indomethacin given after 24 hours of life for closure of a symptomatic PDA. All doses and durations of any continuous infusion were included. Control group: Indomethacin administered as a bolus dose of no longer than 20 minutes in any dosing schedule after 24 hours of life for closure of a symptomatic PDA. 2 RCTs/quasi RCTs met inclusion criteria including 40 preterm infants (25 to 32 weeks gestational age) less than 1750 g birth weight.</td>
<td>To compare continuous infusion to intermittent bolus injection (Relative Risk [RR] was reported). PDA closure at day 2 (RR 1.57, 95% CI 0.54, 4.60). PDA closure at day 5 (RR 2.77, 95% CI 0.33, 23.14). RR&gt;1 favours IV indomethacin bolus.</td>
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</table>

**Authors’ conclusions**

Due to a paucity of events and lack of precision, the available data was found to be insufficient to draw conclusions regarding the efficacy of continuous indomethacin infusion versus bolus injections for the treatment of PDA. Although continuous indomethacin seems to cause less alterations in cerebral, renal and mesenteric circulations, the clinical meaning of this effect is unclear. Definitive recommendations about the preferred method of indomethacin administration i.e. continuous versus bolus infusions for the treatment of PDA in premature infants cannot be made based on the current findings of this review.
Objectives & Criteria

To compare the efficacy and safety of bolus injection to slow infusion of indomethacin on the intermittent dosing protocols in common practice (0.2, 0.1-0.25x2mg/kg/12-24hr x 1-2 courses).

This systematic literature review includes reported randomised, quasi-randomised controlled trials and retrospective & prospective cohort-series on the use of intermittent slow infusion and intermittent bolus injection of indomethacin for closure of a haemodynamic PDA in preterm infants diagnosed clinically and/or by echocardiography.

Treatments, Studies & Patients

A total of 99 distinct clinical study reports were included in the review, 46 reporting on bolus and 53 on slow infusion dosing. There were:

- 35 RCTs including 1185 subjects: 474 treated by bolus and 711 by slow infusion;
- 32 prospective case series studies including 860 subjects: 272 treated by bolus and 588 by slow infusion;
- 32 retrospective case series studies including 2218 subjects: 595 treated by bolus and 1623 by slow infusion.
- Some of the studies had “titrated to response schedules”, the latter schedules employing echocardiography to confirm that the PDA had not closed prior to each dose.

Primary Results by Endpoint

To compare intermittent bolus injection to slow infusion (rate of PDA closure after 1st course, rate of PDA closure after allocated treatment, rate of surgical ligation after allocated treatment were reported for each method of administration).

For the pooled efficacy estimates there are no significant differences between the bolus and slow infusion groups (p>0.05). Rate estimates (95%CI) for all studies included in the review on the primary outcome of PDA closure after 1st course (bolus vs slow) were 72.2% (67.4% to 77.0%) vs 70.7% (63.8% to 77.6%), p=0.728. Estimates for all studies included in the review on the secondary outcomes of PDA closure and surgical ligation after allocated treatment (bolus vs slow) were 79.9% (76.1% to 83.7%) vs 78.8% (75.0% to 82.6%), p=0.687 and 12.7% (8.5% to 16.9%) vs 12.7% (9.3% to 16.1%), p=1.000.

Estimates for the primary and secondary outcomes by treatment regimen and mean cumulative dose are provided in Table 2.

Of the key toxicity measures reported from a reasonable number of studies, the following measures occurred less frequently in the Bolus group, NEC [5.0% (2.7% to 7.3%) vs 10.4% (7.1% to 13.7%), p=0.012], Any ICH [2.0% (0.4% to 5.8%) vs 9.0% (4.3% to 13.7%); p=0.002] and ventilatory support [5.0% (1.4% to 12.3%) vs 35.9% (24.6% to 47.2%); p<0.001].

Estimates for key toxicity outcomes by treatment regimen are provided in Tables 3 and 4.

The review did not find differences between bolus and slow infusions for decreases in cerebral or mesenteric blood flow. There was no deterioration in cerebral function demonstrated for either method of administration.

Summary of Authors’ conclusions

The review indicated that the infusion of indomethacin over 15 to 30 minutes in doses of 0.2, 0.1-0.25 every 12-24hrs was at least as effective as bolus administration in promoting ductal closure in preterm infants and does not increase the risk of any of the monitored complications.

Company Comment
The conclusions of the authors that slow infusion of indomethacin does not increase the risk of any of the monitored complications is an opinion based on the strength of the available data but, as indicated in the table above, some of the key toxicity measures (NEC, ICH & ventilator support) reported did occur less frequently in the bolus group.

Estimates for the primary (PDA closure after first treatment course) and secondary (PDA closure and surgical ligation after allocated treatment) outcomes by treatment regimen and mean cumulative dose arising from the Merck, Sharp & Dohme 2008 review are provided in Table 2. The results for all studies (observational + RCTs) within the dose range recommended for prescribing are shown non-bolded while the results for pooled RCTs are shown bolded. The studies which examined the use of indomethacin titrated to response (indomethacin treatment guided by the PDA flow pattern) were reviewed separately to the standard 3 dose course schedules.

Table 2
Comparative efficacy results (% event rate of PDA closure or surgical ligation, with corresponding 95% CI) for each method of administration: MSD 2008 review

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Closure after 1st Course</th>
<th>Closure after Allocated Treatment (assessed at end of treatment)</th>
<th>Surgical Ligation after Allocated Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus</td>
<td>Slow</td>
<td>Bolus</td>
</tr>
<tr>
<td><strong>Dose range covered by Product Information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2-0.1-0.25mg/kg/12h-24h</td>
<td>0.66(0.56,0.75)</td>
<td>0.70(0.62,0.77)</td>
<td>0.76(0.68,0.85)</td>
</tr>
<tr>
<td></td>
<td>0.67(0.57,0.78)</td>
<td>0.68(0.52,0.83)</td>
<td>0.75(0.68,0.81)</td>
</tr>
<tr>
<td><strong>Dose schedules covered by Product Information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2mg/kg/12h (≤ 3 doses)</td>
<td>0.60(0.43,0.77)</td>
<td>0.68(0.58,0.78)</td>
<td>0.75(0.68,0.82)</td>
</tr>
<tr>
<td></td>
<td>0.58(0.42,0.75)</td>
<td>0.67(0.50,0.85)</td>
<td>0.75(0.47,0.93)</td>
</tr>
<tr>
<td>0.2mg/kg/12h (3 doses ≤ 6)</td>
<td>0.69(0.42,0.96)</td>
<td>0.79(0.73,0.84)</td>
<td>0.79(0.73,0.84)</td>
</tr>
<tr>
<td></td>
<td>0.64(0.54,0.75)</td>
<td>0.82(0.75,0.88)</td>
<td>[0.76/0.79mg/kg]</td>
</tr>
<tr>
<td>0.2mg/kg/24h (≤ 3 doses)</td>
<td>0.78(0.65,0.90)</td>
<td>0.92(0.86,0.98)</td>
<td>0.77(0.72,0.72)</td>
</tr>
<tr>
<td></td>
<td>0.73(0.47,0.98)</td>
<td>[0.62mg/kg]</td>
<td>[0.78mg/kg]</td>
</tr>
<tr>
<td>0.2mg/kg/24h (3 doses ≤ 6)</td>
<td>0.81(0.73,0.89)</td>
<td>0.12(0.00,0.28)</td>
<td>0.12(0.00,0.28)</td>
</tr>
<tr>
<td>0.2mg/kg/12-24h (≤ 3 doses)</td>
<td>0.79(0.70,0.87)</td>
<td>0.82(0.67,0.97)</td>
<td>0.90(0.82,0.99)</td>
</tr>
</tbody>
</table>
There were no significant differences between the two methods of administration (bolus and slow infusion) on all studies combined for the dose range and treatment schedules recommended for prescribing. This pattern is consistent for the primary and secondary outcomes.

Of the efficacy measures reported from a reasonable number of studies on the pooled subset of RCT studies (bolded), comparability between the bolus and slow infusion groups on the primary outcome (PDA closure after 1st course) was demonstrated for all studies combined, the standard treatment regimen 0.2mg/kg/12h (≤ 3 doses) and titrated schedules. With respect to the secondary outcomes (PDA closure and surgical ligation after completion of allocated treatment result) comparability between the bolus and slow infusion groups was observed on all studies combined and the treatment schedules 0.2mg/kg/12h (≤ 3 doses) for PDA closure after allocated treatment and on the 0.2mg/kg/12h (3 < doses ≤ 6) schedule for ligation after allocated treatment. A statistically superior result on PDA closure after allocated treatment was found for the slow infusion group on the 0.2mg/kg/12h (3 doses ≤ 6). The precision of this finding does require some caution due to the small number of studies (low statistical power) included in this comparison (bolus, n=3 studies, 91 patients) vs (slow, n=12, 437 patients).

The titrated dosage treatment schedules yielded statistically superior primary treatment outcome (closure after 1st course) on all studies combined compared to non-titrated bolus (p<0.01) and slow infusion (p<0.05) for the dose range prescribed in the Product Information.

**Systematic Review Comparing Prophylactic Indomethacin Therapy to Indomethacin Therapy for Symptomatic PDA**

A previous meta-analysis of randomised studies comparing prophylactic indomethacin therapy versus indomethacin therapy for symptomatic PDA demonstrated short-term benefits with prophylactic therapy. These benefits included a reduction in the incidence of PDA, need for surgical ligation of a PDA, and severe IVH without increased risk of intestinal or renal side effects. Despite these reported short-term benefits, published survey findings on clinical practice suggest that about seventy five percent of NICUs use indomethacin therapy for symptomatic PDA and not prophylactically for asymptomatic PDA. One plausible explanation for this difference could be the perceived possibility by the physician of spontaneous closure of asymptomatic PDA and lack of long-term benefits with prophylactic indomethacin. Further RCTs have been recommended to assess more precisely its beneficial and adverse effects on short and long-term outcomes.

Overall, the findings from the systematic reviews on Indomethacin therapy for symptomatic PDA indicated:

- Prolonged indomethacin course does not appear to have a significant effect on improving important outcomes, such as PDA treatment failure, CLD, IVH, or mortality. The reduction of transient renal
impairment does not outweigh the increased risk of NEC associated with the prolonged course. Based on these results, a prolonged course of indomethacin cannot be recommended for the routine treatment of PDA in preterm infants (Herrera 2008).

- The available data was found to be insufficient to draw conclusions regarding the efficacy of continuous indomethacin infusion versus bolus injections for the treatment of PDA. Although continuous indomethacin seems to cause less alterations in cerebral, renal and mesenteric circulations, the clinical meaning of this effect is unclear. Definitive recommendations about the preferred method of indomethacin administration i.e. continuous versus bolus infusions for the treatment of PDA in premature infants could not be made based on the current findings of this review (Görk 2008).

- The infusion of indomethacin over 15 to 30 minutes in doses of 0.2, 0.1-0.25, 0.1-0.25 every 12-24hrs was at least as effective as bolus administration in promoting ductal closure in preterm infants and does not increase the risk of any of the monitored complications (MSD 2008).

- Indomethacin treatment guided by the PDA flow pattern (titrated to response) is as good as the standard indomethacin treatment protocol in terms of ductal closure and is associated with significantly fewer doses of indomethacin than normal. Furthermore, fewer doses were associated with a reduced rate of complications - hypoglycaemia, impaired urine output, and gastrointestinal bleeding. There was no obvious effect on neonatal morbidity or the incidence of chronic lung disease (MSD 2008).

Evidence from controlled trials comparing outcomes on infants treated after or in adjunct to conservative treatment with infants whose treatment was commenced early with indomethacin suggests no advantage is conferred by delaying indomethacin treatment. A haemodynamically significant PDA in extremely preterm infants can lead to serious respiratory, intestinal and neurological morbidities, and a delay in indomethacin therapy needs careful justification (MSD 2008).

- Significant differences in mortality rate and transient urine output for the pooled randomised clinical trials for the dose range recommended for prescribing were observed with bolus treatment as compared to slow infusion, with a higher incidence of mortality (and an improved incidence of transient urine output) observed on bolus injection. No significant difference is demonstrated when the same analysis is further broken down into treatment dosage schedules as measured for any of the safety outcomes including mortality, transient renal output and transient Serum Creatinine. On the dose range recommended for prescribing for all studies combined, the measures NEC, GI Perforation and GI Bleeding were shown to occur less frequently on the bolus delivery. Of the toxicity measures reported from an adequate number of studies, the following measures occurred less frequently in the Bolus group: NEC, Any ICH and ventilatory support.

Indications

Indomethacin Agila is indicated for the closure of patent ductus arteriosus in premature babies. Clear-cut clinical evidence of a haemodynamically significant patent ductus arteriosus should be present, such as respiratory distress, a continuous murmur, a hyperactive precordium, cardiomegaly and pulmonary plethora on chest x-ray. Indomethacin Agila should only be used in a hospital under supervision of a specialist neonatologist.

Contraindications

Indomethacin Agila is contraindicated in infants with established or suspected untreated infection; infants who are bleeding, especially with active intracranial haemorrhage or gastro-intestinal bleeding; infants with congenital heart disease in whom patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow (e.g. pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta); infants with thrombocytopenia; infants with coagulation defects; infants with known or suspected necrotising enterocolitis; infants with significant impairment of renal function.
Precautions

Gastrointestinal Effects

Clinical results indicate that major gastrointestinal bleeding was no more common in those infants receiving indomethacin than in those infants on placebo. However, gastrointestinal bleeding (i.e. chemical detection of blood in the stool) was more commonly noted in those infants treated with indomethacin.

Severe gastrointestinal effects have been reported in adults with various arthritic disorders treated chronically with oral indomethacin. These include gastrointestinal bleeding, vomiting, abdominal distention, melena, transient ileus, gastric perforation, localised perforation(s) of the small and/or large intestine, necrotising enterocolitis.

Data in adults indicate that all NSAIDs can cause gastrointestinal discomfort and serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 – 6 months and in about 2 – 4% of patients treated for one year.

These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients or their guardians about the signs and symptoms or serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increases the risk or serious gastrointestinal adverse events.

CNS Effects

Prematurity per se, is associated with an increased incidence of spontaneous intraventricular haemorrhage. Because indomethacin may inhibit platelet aggregation, the potential for intraventricular bleeding may be increased.

Renal Effects

Indomethacin may cause significant reduction in urine output with concomitant elevations of blood urea nitrogen and creatinine, and reductions in glomerular filtration rate and creatinine clearance. These effects in most infants are transient, disappearing with cessation of therapy with indomethacin. However, because adequate renal function can depend upon renal prostaglandin synthesis, indomethacin may precipitate renal insufficiency, including acute renal failure, especially in infants with conditions such as extracellular volume depletion from any cause, congestive heart failure, sepsis, concomitant use of nephrotoxic drugs or hepatic dysfunction. When significant suppression of urine volume occurs after treatment no additional dose should be given until the urine output returns to normal levels.

Indomethacin in pre-term infants may suppress water excretion to a greater extent than sodium excretion. This may result in hyponatraemia. Renal function and plasma electrolytes should be monitored (see Precautions, Drug Interactions and Dosage and Administration).

Cardiovascular Thrombotic Events

Observational studies in adults have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).
There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

**Hypertension**

Studies in adults have indicated that NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

**Heart failure**

Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention or heart failure. This information is based on data in adult patients.

**Severe Skin Reactions**

Data in adults indicate that NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and independent of dose or duration of use. Patients or their guardians should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

**General**

Indomethacin may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection.

Severe hepatic reactions including jaundice and hepatitis have been reported on rare occasions in adults treated chronically with oral indomethacin for arthritic disorders. If clinical signs and symptoms consistent with liver disease develop in the neonate, or if systemic manifestations occur, indomethacin should be discontinued.

Indomethacin may inhibit platelet aggregation and therefore premature infants receiving the drug should be observed closely for signs of bleeding.

Indomethacin should be administered carefully to avoid extravasation and resultant irritation to tissues.

**Interactions with other Medicines**

**Cardiac Glycosides**

Since renal function may be reduced by indomethacin, consideration should be given to reduction in dosage of those medications that rely on adequate renal function for their elimination. The half-life of digitalis in premature babies with patent ductus arteriosus and with cardiac failure can be prolonged by indomethacin. When both drugs are used concomitantly, frequent monitoring of ECG and serum digitalis may help prevention or early detection of digitalis toxicity.

**Aminoglycosides**

In a study of premature infants treated with indomethacin and also receiving either gentamicin or amikacin, both peak and trough levels of these aminoglycosides were significantly elevated.

**Diuretics**

Indomethacin may reduce diuretic effects, including the diuretic effect of furosemide.

Therapy with indomethacin may blunt the natriuretic effect of furosemide and help maintain renal function in the premature infant when indomethacin is added to the treatment of patent ductus arteriosus. This response has been attributed to inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory drugs. This effect however has not been consistently observed with some studies suggesting that furosemide may not prevent deterioration in renal function when administered with indomethacin (Romagnoli 1997, Struis 2003). Romagnoli (1997) found that furosemide cannot prevent indomethacin-induced renal failure, but it does not have any negative influence on its therapeutic effectiveness. Struis (2003) concluded that the additional use of furosemide to indomethacin did not compromise ductal closure, but did result in a significant hyponatremia and in an unexpected increase of serum creatinine without marked influence on the urine output. By contrast, in a study
of 19 premature infants with patent ductus arteriosus treated with either indomethacin alone or a combination
of indomethacin and frusemide, results showed that infants receiving both indomethacin and frusemide had
significantly higher urinary output, higher levels of sodium and chloride excretion, and higher glomerular
filtration rates than did those infants receiving indomethacin alone. In this study, the data suggested that
therapy with frusemide helped to maintain renal function in the premature infant when indomethacin was added
to the treatment of patent ductus arteriosus Yeh 1982.

Indomethacin causes marked reduction of glomerular filtration rate and creatinine clearance for 24-96 hours.
All drugs relying on renal excretion should be avoided during this period or should be monitored with plasma
levels and dose modification accordingly.

Anticoagulants
Indomethacin usually does not influence the hypoprothrombinemia produced by anticoagulants. When
indomethacin is added to anticoagulants, prothrombin time should be monitored closely. In post marketing
experience, bleeding has been reported in patients on concomitant treatment with anticoagulants and
indomethacin. Caution should be exercised when indomethacin and anticoagulants are administered
concomitantly.

Antihypertensive medications
In some patients with compromised renal function, the co-administration of an NSAID and an ACE inhibitor
may result in further deterioration of renal function, including possible acute renal failure, which is usually
reversible.

Aspirin
The use of indomethacin with aspirin or other salicylates is not recommended.

Other NSAIDs
The concomitant use of indomethacin with other NSAIDs is not recommended due to the increased possibility
of gastro-intestinal toxicity, with little or no increase in efficacy.

Corticosteroids
In a study of premature infants treated with indomethacin, concurrent use of corticosteroids appeared to
increase the risk of NEC.

Neonatal Effects
There is a lack of long-term follow-up studies of babies who have received indomethacin in controlled trials.
Further studies examining the long-term safety of indomethacin are required. In view of the widespread
prostaglandin inhibiting effects of indomethacin, and immaturity of the very low birthweight population, the
results of any studies need to be interpreted with caution, especially in comparison with surgical ligation.

In rats and mice, oral indomethacin 4.0 mg/kg/day given during the last three days of gestation caused a
decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal
tissue loss in the diencephalon in the liveborn fetuses was observed. At 2.0 mg/kg/day, no increase in neuronal
necrosis was observed as compared to the control groups. Administration of 0.5 or 4.0 mg/kg/day during the
first three days of life did not cause an increase in neuronal necrosis at either dose level.

Pregnant rats, given 2.0 mg/kg/day and 4.0 mg/kg/day during the last trimester of gestation, delivered offspring
whose pulmonary blood vessels were both reduced in number and excessively muscularised. These findings
are similar to those observed in the syndrome of persistent pulmonary hypertension of the newborn.

Adverse Effects
The following tables compare the toxicities of indomethacin bolus vs slow infusion (15-30mins) for the
individual dose schedules and overall dose range (0.2, 0.1-0.25x2mg/kg/12-24hr x1-2 courses) recommended
for prescribing arising from the Merck, Sharp & Dohme 2008 review.

Aggregate results for all studies or pooled estimates (observational + RCTs) on the dose range recommended
for prescribing are shown non bolded while the results for pooled RCTs are shown bolded.
# Table 3

Comparative safety results on Mortality & Renal Toxicity (% event rate or mean estimate, with corresponding 95% CI) for each method of administration: MSD 2008 review

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Mortality Rate</th>
<th>Transient Urine Output</th>
<th>Transient SeCr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus</td>
<td>Slow</td>
<td>Bolus</td>
</tr>
<tr>
<td>Dose range covered by Product Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2-0.1-0.25mg/kg/12h-24h</td>
<td>0.10(0.06,0.15)</td>
<td>0.08(0.05,0.10)</td>
<td>1.79(0.57,3.01)</td>
</tr>
<tr>
<td>0.13(0.06,0.21)</td>
<td>0.05(0.02,0.08)***</td>
<td>2.48(0.95,4.01)</td>
<td>2.25(1.94,2.56)**</td>
</tr>
<tr>
<td>Dose schedules covered by Product Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2x3mg/kg/12h-≤3 doses</td>
<td>0.06(0.00,0.19)</td>
<td>0.04(0.01,0.08)</td>
<td></td>
</tr>
<tr>
<td>0.00(0.00,0.20)</td>
<td>0.04(0.00,0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2x3mg/kg/12h3&lt; doses ≤6</td>
<td>0.09(0.00,0.18)</td>
<td>0.08(0.04,0.11)</td>
<td>2.25(1.94,2.56)</td>
</tr>
<tr>
<td>0.11(0.00,0.26)</td>
<td>0.04(0.01,0.07)</td>
<td>2.25(1.94,2.56)</td>
<td>1.16(1.06,1.26)</td>
</tr>
<tr>
<td>0.2x3mg/kg/24h-≤3 doses</td>
<td>0.17(0.00,0.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.31(0.09,0.61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2x0.1-0.1mg/kg/12h 3&lt; doses≤6 s</td>
<td></td>
<td></td>
<td>0.26(0.12,0.45)</td>
</tr>
<tr>
<td>0.13(0.06,0.21)</td>
<td>0.10(0.00,0.21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.01 (relative to Bolus equivalent schedule); ** p < 0.001 (relative to Bolus equivalent schedule). >3 doses ≤ 6 means the number of doses administered was more than 3 and 6 doses or less.

The pooled safety results on all studies combined for the dose range recommended for prescribing showed comparability between the bolus and slow infusion groups for mortality and renal toxicity. By treatment regimen, comparability on mortality rates between the bolus and slow infusion groups was observed for all studies for the schedules 0.2x3mg/kg/12h-≤ 3 doses and 0.2x3mg/kg/24h-≤ 3 doses.

Significant differences in mortality rate and transient urine output for the pooled RCTs (highlighted in bold) for the dose range recommended for prescribing were observed with bolus treatment as compared to slow infusion with a higher incidence of mortality (and an improved incidence of transient urine output) observed on bolus injection. The difference in the mortality analysis can be attributed to the change in treatment protocols since the introduction of the bolus modality in the 1970's which have since been superseded by more modern practice. In particular we refer to the time lag bias arising from significant technological improvements to the present slow infusion era and the delayed pharmacological treatment of the Bolus infants until after Usual Management Therapy has failed (on average 8 days from birth). Examination of the baseline characteristics of the RCTs included in the mortality analysis show significant differences between the infants in the Bolus and Slow groups for age at 1st dose, gestational age and mean cumulative dose. Of these the difference of most clinical relevance was age at 1st dose (increased for Bolus, p<0.0001).

No significant difference is demonstrated when the same analysis is further broken down into treatment dosage schedules as measured for any of the safety outcomes including mortality, transient renal output and transient Serum Creatinine.
Table 4
Comparative safety results on Gastrointestinal Toxicity (% event rate with corresponding 95% CI) for each method of administration: MSD 2008 review

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>NEC</th>
<th>GI Perforation</th>
<th>GI Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus Slow</td>
<td>Bolus Slow</td>
<td>Bolus Slow</td>
</tr>
<tr>
<td>Dose range covered by Product Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2,0.1-0.25mg/kg/12h-24h</td>
<td>0.05(0.02,0.07)</td>
<td>0.10(0.07,0.13)</td>
<td>0.04(0.03,0.06)</td>
</tr>
<tr>
<td>Dose schedules covered by Product Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2x3mg/kg/12h≤3 doses</td>
<td>0.00(0.00,0.20)</td>
<td>0.07(0.00,0.15)</td>
<td></td>
</tr>
<tr>
<td>0.2x3mg/kg/12h-3 &lt; doses ≤6</td>
<td>0.05(0.02,0.09)</td>
<td>0.04(0.00,0.09)</td>
<td>0.04(0.02,0.06)</td>
</tr>
<tr>
<td>0.2x3mg/kg/24h≤3 doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2x3mg/kg/12-24h≤3 doses</td>
<td>0.06(0.00,0.12)</td>
<td>0.08(0.04,0.12)</td>
<td></td>
</tr>
<tr>
<td>0.2x3mg/kg/12-24h 3 &lt; doses≤6</td>
<td>0.11(0.01,0.33)</td>
<td>0.10(0.05,0.15)</td>
<td></td>
</tr>
<tr>
<td>0.2.0,1.0,1mg/kg/12-24h 3 &lt; doses ≤6</td>
<td></td>
<td>0.17(0.02,0.31)</td>
<td></td>
</tr>
<tr>
<td>Titated to response dose schedules</td>
<td>0.06(0.00,0.13)</td>
<td>0.10(0.05,0.14)</td>
<td>0.00(0.00,0.10)</td>
</tr>
</tbody>
</table>

p < 0.05 (relative to Bolus equivalent schedule); **p < 0.01 (relative to Bolus equivalent schedule)

NEC, necrotising enterocolitis. >3 doses ≤6 means the number of doses administered was more than 3 and 6 doses or less.

On the dose range recommended for prescribing for all studies combined, the measures NEC, GI Perforation and GI Bleeding were shown to occur less frequently on the bolus delivery. The findings were statistically significant for the NEC and GI perforation measures (p<0.05). By treatment regimen, for all studies combined there was comparability between the bolus and slow infusion groups on GI toxicity measures for all treatment schedules on which a reasonable number of studies were available. Within the subset of RCTs, comparability was observed between the bolus and slow infusion groups on all measures for all studies combined on the dose range recommended for prescribing. GI bleeding was observed in the RCT subset at a higher incidence in the bolus injection group on the 0.2x3mg/kg/12h 3 < doses ≤6 schedule. This finding should be viewed cautiously due to the small number of studies (low statistical power) included in this comparison (Bolus, n=1 studies, 62 patients) vs (Slow, n=3, 113 patients).
The following adverse reactions in infants treated with indomethacin have been reported in the medical literature, regardless of the route of administration.

**Renal**

(Incidence rates from literature - acute renal failure 3.2%; oliguria 44%)

Renal dysfunction including one or more of the following: reduced urinary output; reduced urine sodium, chloride, or potassium, urine osmolality, free water clearance, or glomerular filtration rate; uraemia, transient oliguria, and hypercreatininaemia. Electrolyte disturbances are common following indomethacin in preterm neonates. The risk of renal impairment appears to be dose related. The impaired renal function usually resolves over 24 hours following discontinuation.

**Gastrointestinal**

(Incidence rates from literature – GI bleeding 3.9% to 7.6%; Perforation 2.2%; NEC 4.6% to 7.7%)

Gastrointestinal bleeding, vomiting, abdominal distention, melaena, transient ileus, gastric perforation and, localised perforations of the small and/or large intestine, necrotising enterocolitis.

**Haemorrhagic**

(Incidence rates from literature – bleeding 10%).

Gross or microscopic bleeding into the gastro-intestinal tract, oozing from the skin after needle puncture, pulmonary haemorrhage, and disseminated intravascular coagulopathy.

**Cerebral**

(Incidence rates from literature – PVL 6.5%; ICH 7.1% to 10.5%; IVH 8.6% to 14.3%)

Periventricular leukomalacia, intracranial haemorrhage, intraventricular haemorrhage have been reported in Randomised Clinical Trials with the slow infusion regimen.

**Metabolic**

Hypersensitivity, hyponatraemia, elevated plasma potassium, elevated blood urea, hypoglycaemia, decreased platelet aggregation and reduction in blood sugar, including hypoglycaemia.

**Coagulation**

Decreased platelet aggregation.

**Cardiovascular**

Pulmonary hypertension; intracranial bleeding.

**Severe Skin Reactions**

Data in adults indicate that NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

**General**

Exacerbation of infection and weight gain (fluid retention).

**Causal relationship unknown**

Although the following adverse reactions have been reported in infants treated with indomethacin, a causal relationship to therapy with indomethacin has not been established.

- **Cardiovascular**: bradycardia.
- **Respiratory**: Apnoea, exacerbation of pre-existing pulmonary infection.
Metabolic - Acidosis/alkalosis.

Haematologic - Disseminated intravascular coagulation.

Ophthalmic (incidence ROP 11.7% to 21.1%; blindness <1%) - Retrolental fibroplasia.

Oedema, hypertension and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

A variety of adverse experiences has been reported in adults treated with oral indomethacin for moderate to severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute painful shoulder and acute gouty arthritis (see section Additional Adverse Effects - Oral Indomethacin - Adults). Their relevance to the pre-term neonate receiving indomethacin for patent ductus arteriosus is unknown.

Additional Adverse Effects - Oral Indomethacin - Adults

The following adverse reactions have been reported in adults treated with oral indomethacin for moderate to severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute painful shoulder and acute gouty arthritis. Complaints not of relevance in the treatment of the premature infant, such as anorexia, psychic disturbances, and blurred vision, are not listed.

Gastrointestinal

(Incidence 1% to 3%)

Diarrhoea; Constipation

(Incidence less than 1%)

Bloating (includes distention), epigastric distress, abdominal pain, flatulence, peptic ulcer, gastroenteritis, rectal bleeding, proctitis; single or multiple ulcerations, including perforation and haemorrhage of the oesophagus, stomach, duodenum or small and large intestines; intestinal ulceration associated with stenosis and obstruction; gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions; development of ulcerative stomatitis; gastritis, toxic hepatitis and jaundice (some fatal cases have been reported).

Central Nervous System

(Incidence less than 1%)

Central nervous system adverse effects are headache, dizziness, light-headedness, depression, vertigo and fatigue (including malaise and listlessness). Reactions reported infrequently include mental confusion, anxiety, syncope, drowsiness, convulsions, coma, peripheral neuropathy, muscle weakness, involuntary muscle movements, insomnia, psychic disturbances such as depersonalisation, psychotic episodes and rarely paraesthesias, dysarthria, aggravation of epilepsy and parkinsonism. These are often transient and disappear frequently with continued treatment or with a reduction in dosage. However, the severity of these may, on occasion, require stopping therapy.

Special Senses

(Incidence less than 1%)

Hearing disturbances, deafness, tinnitus.

Cardiovascular

(Incidence less than 1%)

Hypertension, hypotension, tachycardia, arrhythmia, congestive heart failure, thrombophlebitis, palpitations, chest pain.

Metabolic
(Incidence less than 1%)

Oedema, weight gain, flushing, hyperglycaemia, glycosuria, hyperkalaemia.

**Integumentary**
(Incidence less than 1%)

Rash, pruritus, urticaria, angiitis, petechiae or ecchymosis, exfoliative dermatitis, erythema nodosum, loss of hair, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis.

**Haematologic**
(Incidence less than 1%)

Leucopenia, bone marrow depression, anaemia secondary to obvious or occult gastrointestinal bleeding, aplastic anaemia, haemolytic anaemia, agranulocytosis, thrombocytopenic purpura, thrombocytopenia and disseminated intravascular coagulation. There have been several reports of leukaemia. The supporting information is weak.

**Hypersensitivity**
(Incidence less than 1%)

Acute anaphylaxis, acute respiratory distress, rapid fall in blood pressure resembling a shock-like state, dyspnoea, asthma, purpura, angiitis, pulmonary oedema, angioneurotic oedema.

**Genitourinary**
(Incidence less than 1%)

Haematuria, vaginal bleeding, renal insufficiency including renal failure, proteinuria, nephrotic syndrome, interstitial nephritis, urinary frequency.

**Miscellaneous**
(Incidence less than 1%)

Epistaxis, breast changes (including enlargement and tenderness, or gynaecomastia), ulcerative stomatitis, sweating.

---

**Dosage and Administration**

**INDOMETHACIN AGILA IS FOR INTRAVENOUS ADMINISTRATION ONLY.**

It is recommended that Indomethacin Agila be administered only in a neonatal intensive care-unit.

Indomethacin Agila should not be given without echocardiographic confirmation that symptoms are due to a patent ductus arteriosus and that no other significant cardiac defect exists.

A course of therapy is defined as three intravenous doses of Indomethacin Agila given at 12-24 hour intervals, with careful attention to urinary output. For advice on the rate of infusion see under 'Directions for Use'.

*After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.*

If anuria or marked oliguria (urinary output < 0.6 mL/kg/hr) is evident at the scheduled time of the second or third dose, Indomethacin Agila must not be given until laboratory studies indicate that renal function has returned to normal.

It is likely that a single standard indomethacin regime may not be the ideal for every premature infant. Therefore, individual patient response should be considered and evaluated, in particular in the high risk group of extremely low birth weight babies.
Dosage recommendations for closure of the ductus arteriosus depend closely on the age and weight of the infant at the time of therapy.

<table>
<thead>
<tr>
<th>AGE at 1st Dose</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 48 hours (&lt;1,000 g)</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>2-7 days (&gt;1,000 g)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Over 7 days (&gt;1,000 g)</td>
<td>0.2</td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

If the patent ductus arteriosus closes or is significantly reduced in size 48 hours after the first course of Indomethacin Agila, no further doses are necessary. If the ductus arteriosus re-opens, a second course of 1-3 doses may be given, each dose separated by a 12-24 hour interval as described above.

NCIUs with skilled operators in the use of colour Doppler echocardiography may be guided on indomethacin dosage by the PDA flow pattern arising from echocardiographic examinations performed 12–24 hours daily after birth until the ductus arteriosus closes (MSD 2008, systematic review).

This approach resulted in outcomes as good as the standard indomethacin treatment protocol in terms of ductal closure and was associated with significantly fewer doses of indomethacin than normal (mean cumulative dose: 0.32mg/kg). Furthermore, fewer doses were associated with a reduced rate of complications - hypoglycaemia, impaired urine output, and gastrointestinal bleeding. There was no obvious effect on neonatal morbidity or the incidence of chronic lung disease.

If the infant remains unresponsive to therapy with Indomethacin Agila after 2 courses, surgery may be necessary.

**Directions for Use**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

THE SOLUTION SHOULD BE PREPARED ONLY WITH 1 TO 2 mL OF PRESERVATIVE-FREE STERILE SODIUM CHLORIDE INJECTION BP OR WATER FOR INJECTIONS PH EUR. Preparations containing glucose must not be used.

A fresh solution should be prepared just prior to each administration according to the dilution table below:

<table>
<thead>
<tr>
<th>Amount of diluent used for each vial</th>
<th>Concentration achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mL</td>
<td>0.1 mg/0.1 mL</td>
</tr>
<tr>
<td>2 mL</td>
<td>0.05 mg/0.1 mL</td>
</tr>
</tbody>
</table>

Preservatives should be carefully avoided at every stage because of the risk of toxicity in the newborn; any unused portion remaining in the opened vial should be discarded.

Further dilution with intravenous infusion solutions is not recommended. Indomethacin Agila is not buffered, and reconstitution with solutions at pH values below 6 may result in precipitation of the insoluble indomethacin free acid moiety.

While the optimal rate of injection of Indomethacin Agila has not been established, current published literature suggests slow infusion over 20-30 minutes.
Overdosage

Contact the Poisons Information Centre (In NZ telephone: 0800 764 766 or 0800 POISON) for information regarding overdose management.

The following signs and symptoms have occurred in individuals (not necessarily in premature infants) following an overdose of oral indomethacin: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, lethargy, paraesthesias, numbness and convulsions. There are no specific measures to treat acute overdosage with Indomethacin Agila. The patient should be followed for several days as gastrointestinal ulceration and haemorrhage have been reported as adverse reactions of indomethacin. Any complications occurring in the gastro-intestinal, renal and central nervous system should be treated symptomatically and supportively.

Presentation and Storage Conditions

Indomethacin Agila is presented in single use glass vials containing sterile lyophilised powder for reconstitution. Each vial contains indomethacin sodium trihydrate, equivalent to 1 mg indomethacin.

Indomethacin Agila 1 mg powder for injection is available in cartons containing 3 vials.

Store below 25°C. Protect from light and moisture. Keep in outer carton.

Indomethacin Agila powder for injection is for single use in one patient only. Discard any residue.

Medicine Classification

Prescription Medicine

Name and Address of Sponsor

Mylan New Zealand Ltd
PO Box 11-183
Ellerslie
AUCKLAND
Telephone: 09-579-2792

Date of Preparation

18 September 2014

References


Struis N, Andriessen, Overmeire B V. Furosemide in Preterm Infants Treated with Indomethacin for Patent Ductus Arteriosus.
