CARE IN PEDIATRIC ONCOLOGY

Care in Pediatric Oncology

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1 FORMULATIONS FOR CHILDREN: GUIDELINES AND PRECAUTIONS

The choice of a doctor when prescribing pediatric medications should take into consideration both their effectiveness and the potential adverse effects. Additionally, the child's age, weight, and the development of their body should be taken into consideration (Mello, 2006; Simons; Tibboel, 2006; Hill, 2005; Kearns et al., 2003; Koren, 2003; Burg; Bourret, 1994).

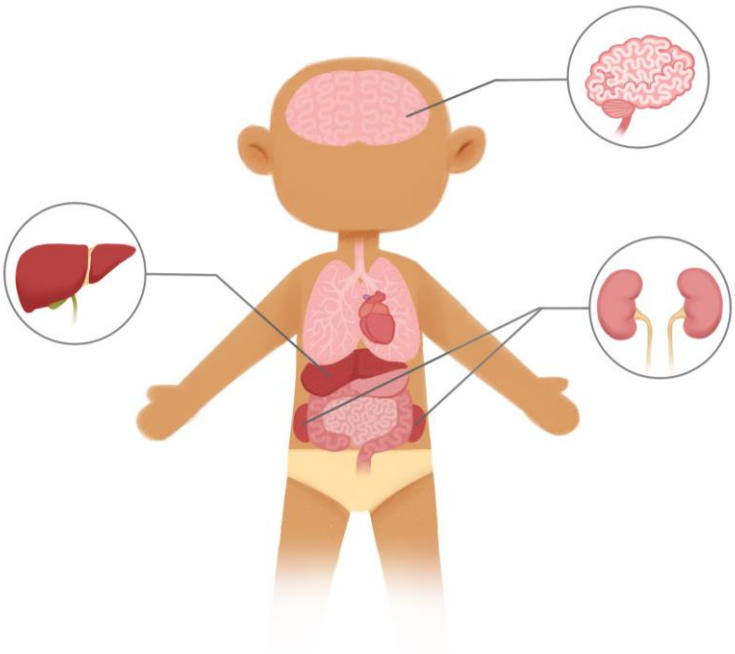
Medications are composed of active components that serve to alleviate pain or prevent vomiting, for example. They also contain other ingredients to provide color, flavor, preservation, and even improve the appearance, making it easier for a child to take the medication (excipients) (Hill, 2005; Balbani et al., 2006; Mello, 2006; Pifferi; Restani, 2003). These excipients are not inert components in the formulation and can potentially cause adverse effects (Balbani et al., 2006; Heineck et al., 2006; Marcovitch, 2005; Pifferi; Restani, 2003).

The functioning of a child's body is different from that of an adult. Therefore, the dosage of medication must be personalised (individualised) according to the child's body composition (Bartelink et al., 2006; Mello, 2006; Simons; Tibboel, 2006; Kearns et al., 2003; Koren, 2003; Burg; Bourret, 1994).

During childhood, the child’s body is maturing. The completion of growth varies individually. In general, by the age of 12, teenagers weigh, on average, around 40 kg and usually tolerate the effects of medications without adverse reactions or with reactions similar to adults. However, some teenagers may begin puberty late and, consequently, finish their growth later than their peers (Figure 1). Therefore, the effects of medications and their excipients vary significantly. Another important factor is that after taking the medication, it must be eliminated (Silva, 2006; Katzung, 2005; Alcorn; McNamara, 2003; Labaune, 1993). To

be eliminated, the medication needs to be broken down into smaller particles, a process mainly handled by the liver (Silva, 2006; Katzung, 2005; Johnson, 2003; Alcorn; McNamara, 2003; Labaune, 1993). Subsequently, elimination occurs through urine or faeces (Silva, 2006; Katzung, 2005; Alcorn; McNamara, 2003; Labaune, 1993).

Figure 2 - The Functioning of a child's body



Special care must be taken with premature babies who need to be hospitalized and take medications, as well as with new borns, as their bodies gradually develop as they grow (Silva, 2006; Simons; Tibboel, 2006; Katzung, 2005; Alcorn; McNamara, 2003; Labaune, 1993).

Treatment should be carried out taking various factors into consideration to prevent adverse effects from the medication or its excipients. Therefore, it's important for the healthcare team to carefully identify which excipients are part of the medication that the child needs to take.

To find out which excipients are present in the formulations, you can check the leaflet or the box of the medication. The excipients will be listed under the "COMPOSITION" section, usually at the beginning of the leaflet, or it may be written on the box or the medication's packaging (Figure 2).

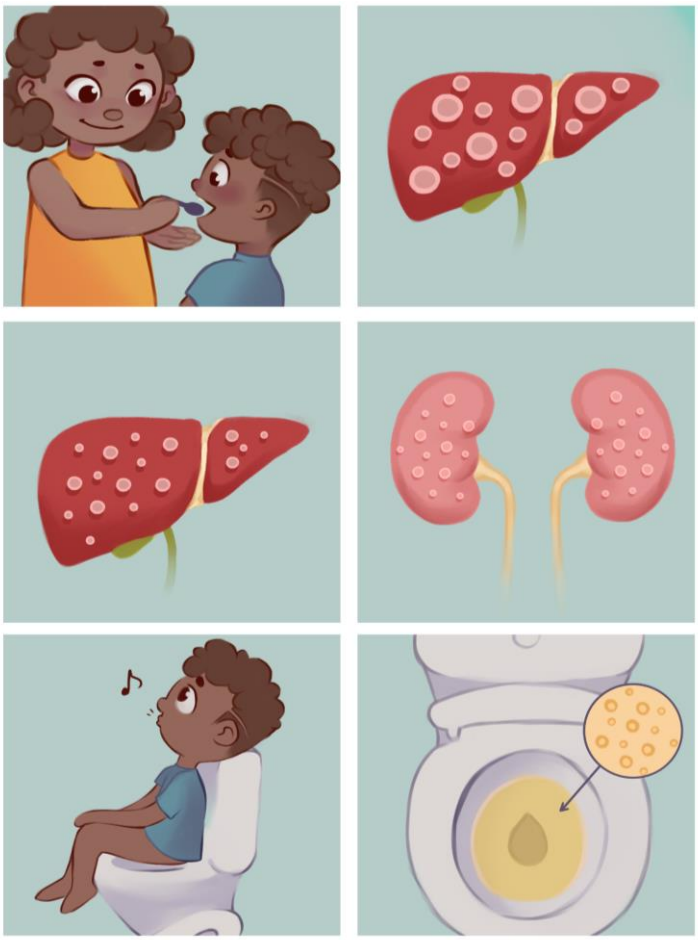
Figure 3 - Mother looking for the composition in the medicine box

2 FOR ORAL USE

For children, especially young ones, the taste of liquid medications should, whenever possible, be pleasant to facilitate their use. Remember that all medications should be kept out of children's reach and should always be administered by a caregiver.

Alcohol is present in some medications for various purposes, such as a solvent (Little, 2004), to dissolve or extend the shelf life. Depending on the child's age, they may have difficulty eliminating alcohol from their system. The younger the child, the more difficult it is for their body to eliminate alcohol. The liver is responsible for breaking down alcohol into smaller pieces for elimination (Johnson, 2003). When a child reaches the age of 12, their kidneys are similar to those of adults, allowing for easier elimination of alcohol through urine (Figure 3).

Figure 4 - Step by step elimination of the medicine from the child's body



Examples of preparations that may contain alcohol include liquid homoeopathic formulations and elixirs. Elixir is not recommended, but alcohol is still used in liquid medications because it is sometimes the only agent that can dissolve many substances in the formulation (Peiré García, 2019).

Just like alcoholic beverages, when taken in large quantities, medicine containing alcohol can have adverse effects, such as dizziness, drowsiness, and speech difficulties. Some serious effects of long-term use of alcohol-containing medicines include poor memory, difficulty breathing, and irregular heartbeat (Rowe et al., 2009; European Medicines Agency, 2006; Klasco, 2006; Kibbe, 2000; Fiocchi et al., 1999).

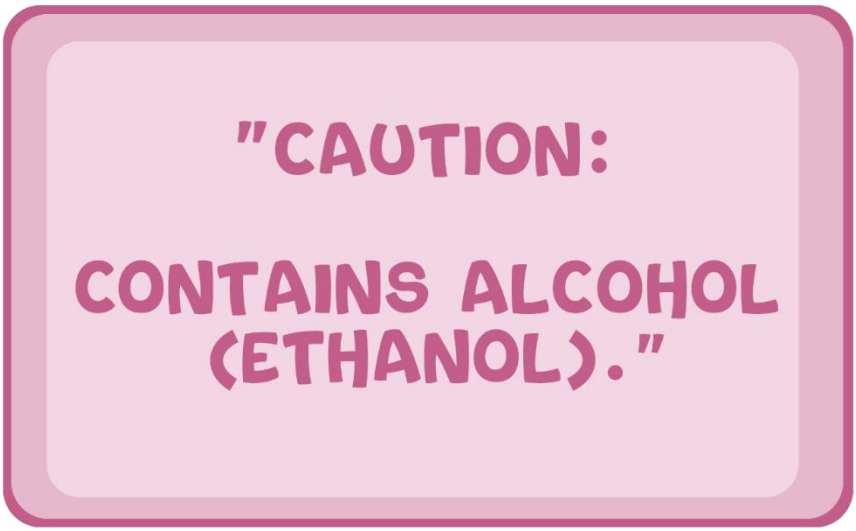
In Brazil, since 2001, the presence of ethanol has been prohibited in appetite stimulants, growth enhancers, tonics, and iron and phosphorus supplements (Figure 4).

Figure 5 - Examples of medicine that may contain alcohol

Vitamins (multivitamins) used for children must have a maximum alcohol content of 0.5%, and the following statement must be included in the product leaflet and label: 'Contains 0.5% ethanol'' (Agência Nacional de Vigilância Sanitária - Anvisa, 2023a, 2022, 2002). Caregivers can find on the product leaflet (Figure 5), label, and box of medications some warnings about the presence of alcohol, so it is important to always consult all of them (Figure 6).

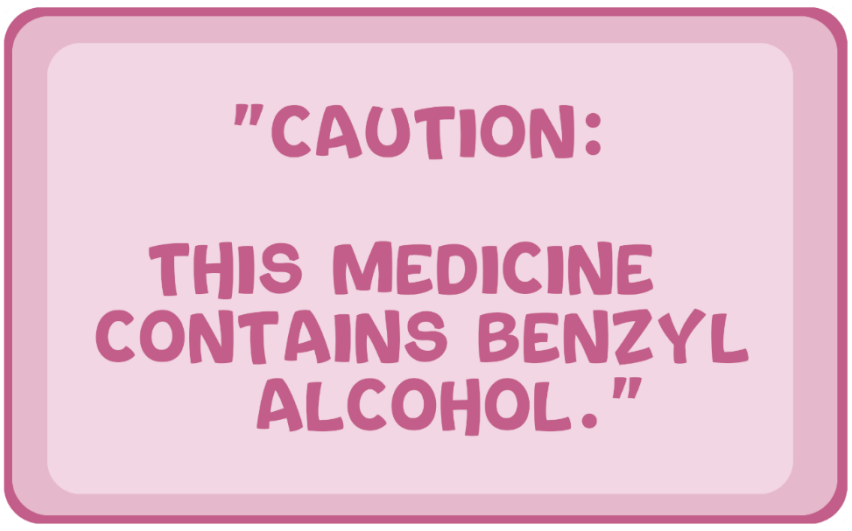
Figure 6 – Leaflet

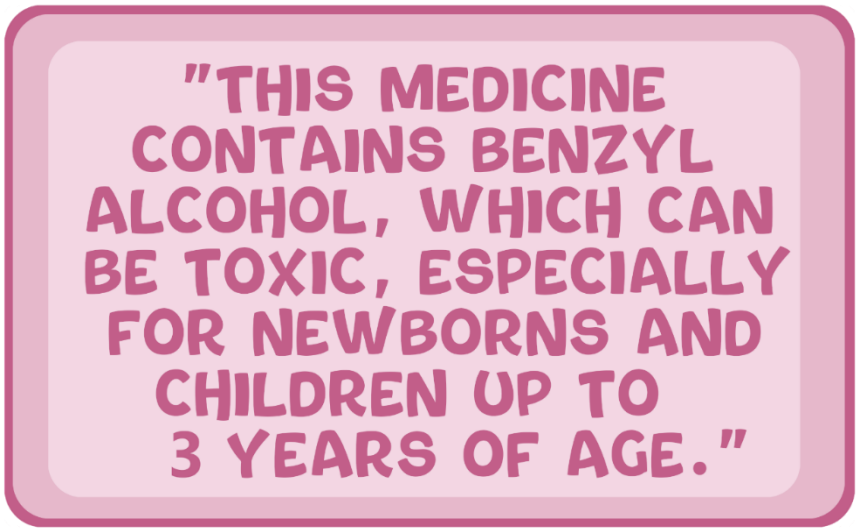
Figure 7 - Warning phrase about the concentration of alcohol in the medicine



Caution should be exercised when using medications that contain benzyl alcohol and its derivatives such as sodium benzoate or benzoic acid in their formulation. The liver is responsible for breaking down benzyl alcohol into smaller pieces for elimination (Johnson, 2003). In newborns, fatal cases of intoxication can occur, along with other adverse effects such as shortness of breath, nausea, and vomiting (Rowe et al., 2009). Benzyl alcohol has also been associated with adverse effects such as wheezing, breathing difficulties, neurological problems, seizures, and low blood pressure (Gershanik et al., 1982). The use of benzyl alcohol is contraindicated in children under 3 years of age (Rowe et al., 2009). The presence of benzyl alcohol will be highlighted, and caregivers can identify it by referring to the medication's leaflet (Figure 7).

Figure 8 – Warning phrase about the concentration of benzyl alcohol in the medicine

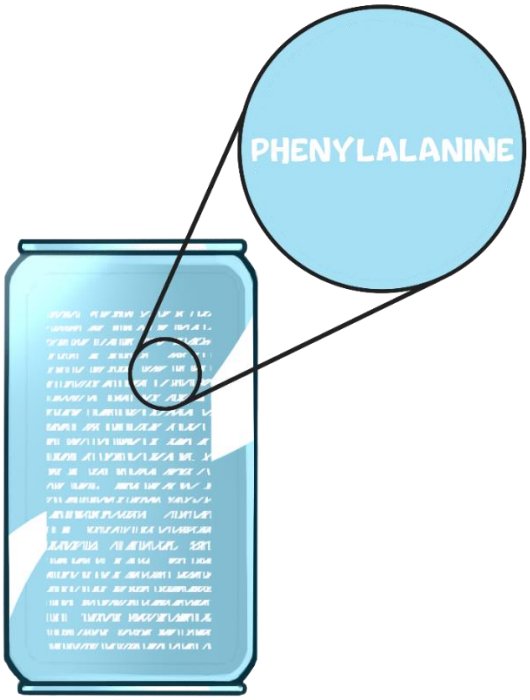




Propylene glycol is another excipient commonly found in medications and can be used as a solvent, among other functions (Kibbe, 2000). In newborns, the liver is immature. The liver is responsible for breaking down propylene glycol into smaller pieces for elimination (Johnson, 2003). Therefore, it takes time to eliminate propylene glycol through urine (European Medicines Agency, 2006; Kibbe, 2000; "Inactive" [...], 1997). Propylene glycol can cause adverse effects such as diarrhea, ear problems, heart problems, neurological problems, kidney problems, abdominal pain, nausea, vomiting, and cramps (European Medicines Agency, 2006; Kibbe, 2000; "Inactive" [...], 1997; Yorgin et al., 1997). Propylene glycol can also affect hormone levels and have adverse effects on the skin (Prusakiewicz et al., 2007; Reisch, 2005).

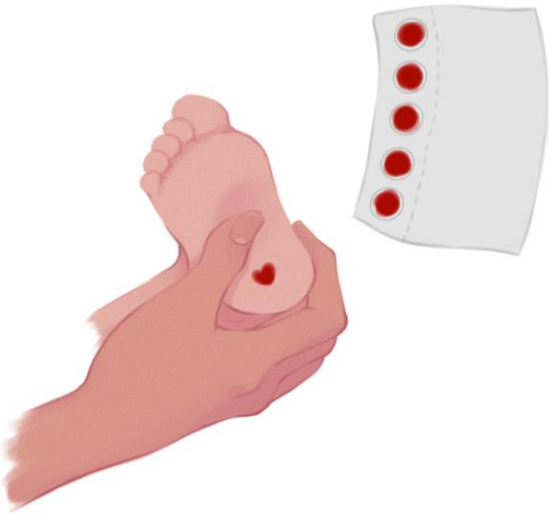
Other components (sweeteners) may be used to sweeten medications, such as sugar, aspartame, cyclamate (Renwick et al., 2004), and saccharin. The main component used to sweeten medications is sugar. Sugar should not be used in children with diabetes (Peres et al., 2005). When it is necessary to use medications with sugar, the insulin doses prescribed for children with diabetes should be adjusted according to medical guidance. If the child can take the medication with sugar, they should brush their teeth immediately afterward to prevent cavities (Neves et al., 2007; Soffritti et al., 2007; Peres et al., 2005). Some medications that contain sugar include pain relievers, cough medicines, antibiotics (Peres et al., 2005), antiparasitic medications, asthma treatments (salbutamol) containing saccharin and cyclamate as sweeteners, and medications for nausea (Soffritti et al., 2007; Peres et al., 2005). Aspartame, which is a sweetener, should not be used by pregnant women as it can pass to the baby and cause adverse effects, including brain problems. An artificial sweetener that may be present in soft drinks is phenylalanine (Figure 8). Pregnant women should avoid consuming soft drinks containing phenylalanine as it can have adverse effects on the baby, especially if the foetus has phenylketonuria, a metabolic disorder.

Figure 9 - Soft drinks that contain phenylalanine (sweetener)



Phenylketonuria is a severe and rare genetic disorder caused by a deficiency of an enzyme called phenylalanine hydroxylase in the child's genetic makeup (Yilmaz et al., 2023). When the enzyme phenylalanine hydroxylase works slowly, the amount of phenylalanine increases in the child's blood and body, which, if left untreated, can lead to serious effects such as reduced brain size, delayed development, seizures, and irreversible behavioural damage. The heel prick test identifies phenylketonuria shortly after birth (Yilmaz et al., 2023) (Figure 9).

Figure 10 - Heel prick test

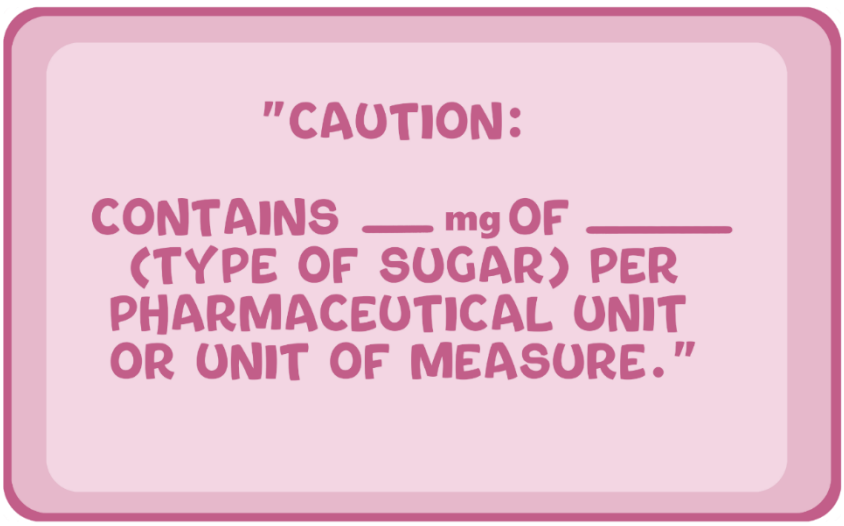


The ingredients used to sweeten medications can be combined, such as saccharin and cyclamate (Renwick et al., 2004). Be aware of adverse effects such as skin allergies or itching when exposed to sunlight (Kibbe, 2000; "Inactive" [...], 1997). Other adverse effects include nausea, diarrhoea, rapid heartbeat, and headaches (Kibbe, 2000; "Inactive" [...], 1997). Mothers should be mindful of the presence of sweeteners like cyclamate and saccharin, whether in food or medications. If the child is taking a sulfa antibiotic, sweeteners like saccharin and cyclamate cannot be used at the same time as sulfa. The simultaneous use of saccharin and cyclamate is contraindicated.

The baby's liver is still developing, and by the age of 2, it's possible to consider that the liver can metabolize medications and sweeteners. It is not recommended to give medications and foods containing cyclamate and saccharin to children under two years of age. Also, be aware that products with cyclamate and saccharin may contain sodium, which can lead to increased blood pressure and eye problems (cataracts) (Renwick et al., 2004).

When a child requires long-term medication for certain medical conditions, it's preferable to choose liquid medications that do not contain sugar in their formula. Various phrases on medication labels may indicate the presence of sucrose (Figure 10). Be sure to check the labels of medications (Anvisa, 2023b).

Figure 11 - Warning phrase about the presence of sugar in medicines



"THIS MEDICATION SHOULD NOT BE USED BY PEOPLE WITH GLUCOSE-GALACTOSE MALABSORPTION SYNDROME."

"THIS MEDICATION SHOULD NOT BE USED BY PEOPLE WITH SUCRASE-ISOMALTASE INSUFFICIENCY."

"CAUTION:

USE WITH CARE IN INDIVIDUALS WITH DIABETES."

Sorbitol is another substance used as a sweetener in medications. It can be found in liquid formulations that do not require shaking (solution) or need to be shaken (suspension). Sorbitol can be used in children with diabetes and does not cause tooth decay, but it can have side effects such as gas, diarrhoea, and abdominal pain (Neves et al., 2007; Balbani et al., 2006; European Medicines Agency, 2006; Peres et al., 2005; Kibbe, 2000). In the body, sorbitol can be converted into another sugar called fructose and should not be used in children with liver problems or low blood sugar (European Medicines Agency, 2006). The presence of sorbitol is indicated in the medication's leaflet and on the pack of the medication (Figure 11).

Figure 12 - Warning phrase about the presence of sorbitol

Preservatives are added to medications in different amounts to maintain the formula's quality and ensure that the medication remains effective until the expiration date indicated on the packaging. Parabens are a group of synthetic compounds made in the laboratory, used

to preserve medications due to their ability to inhibit the growth of bacteria which can contaminate the medication. Parabens include different components, including methylparaben, ethylparaben, propylparabens, and butylparaben. These parabens are the most common (Bethea et al., 2020; Nowak et al., 2018).

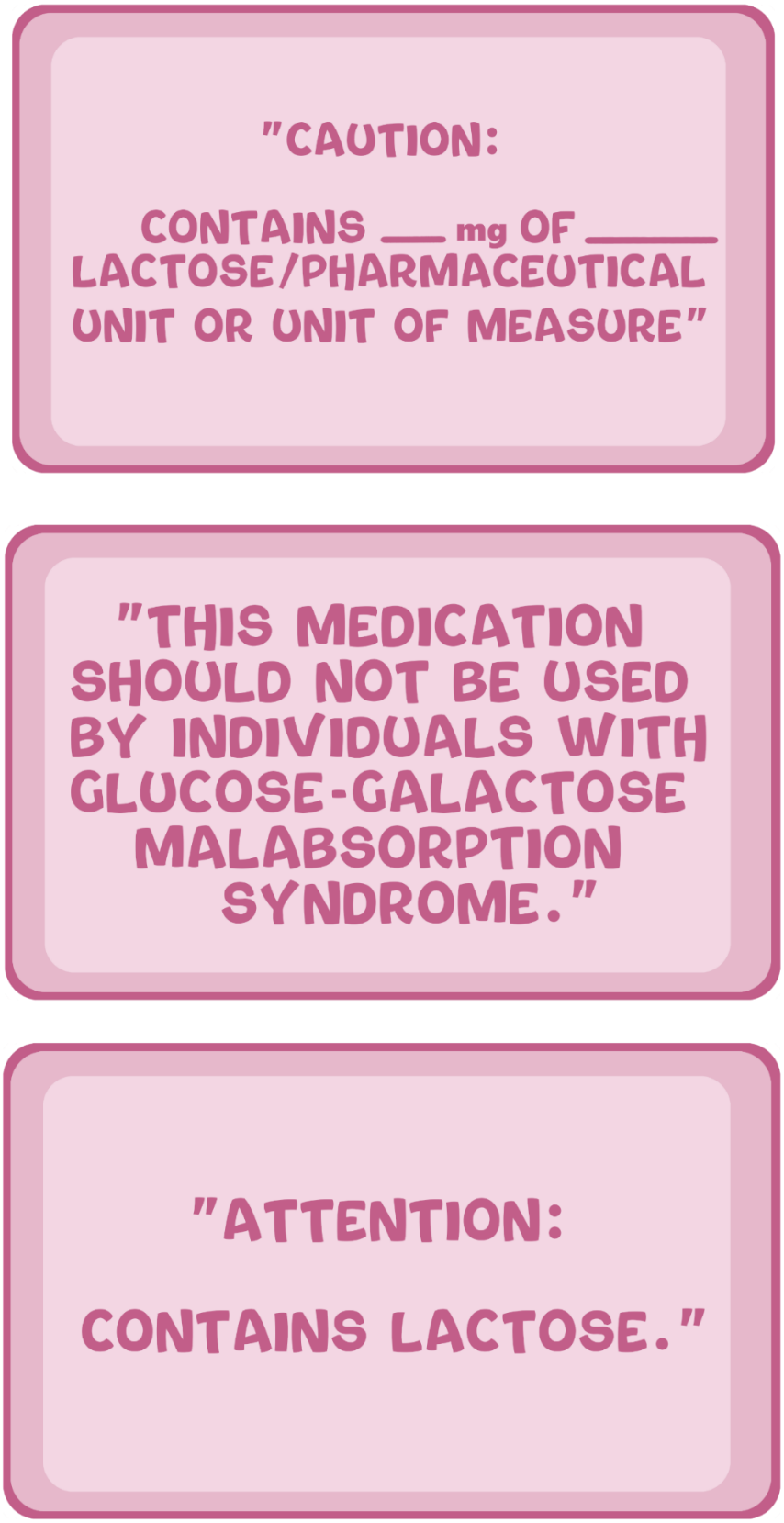
These substances should not be consumed by children until complete pubertal development and at the completion of growth, (adolescents with growth of less than 2 cm in one year, girls with a bone age of 14 years, and boys with a bone age of 16 years). The end of growth does not necessarily coincide with the onset of menstruation in girls and varies individually, depending on skeletal maturation (bone age), which may not always align with chronological age.

Parabens and their derivatives can advance and speed up pubertal development, as well as accelerate bone maturation, leading to the premature conclusion of statural growth. This can result in a child having a shorter stature than the standard average for their family members, for instance, or girls may experience menstruation before the age of 10 (Rosenfield et al., 2020; Cabaleiro et al., 2014). Read the label or leaflet to determine if the medication contains parabens as preservatives. Parabens rarely cause serious allergic reactions (Cabaleiro et al., 2014; Balbani et al., 2006; kibbe, 2000).

Moreover, the use of preparations containing parabens should be avoided during pregnancy because they can pass into breast milk (Dualde et al., 2020). A group of researchers in Spain conducted a study to determine the amount of parabens that pass into breast milk (Dualde et al., 2020). A total of 120 mothers participated in the study, and it was found that breast milk contained 41 to 60% of parabens and 61 to 89% of non-conjugated parabens. It is important to determine the quantity of these preservatives found in breast milk. The estimated daily intake of parabens in breastfeeding newborns ranged from 0 to 10 mg/kg/day, which was considered acceptable (Dualde et al., 2020).

Lactose can also be present in the medication, and it is important to be aware if the child has lactose intolerance, as well as if the child cannot digest galactose, the sugar resulting from the digestion of lactose (galactosemia). Effects like diarrhea, vomiting, nausea, and gas can occur (Pawar; Kumar, 2002). The presence of lactose in orally administered medications will be highlighted in phrases on the leaflet and boxes (Figure 12).

Figure 13 - Warning phrase about the presence of lactose in the medicine



In Brazil, there is a pending bill (PL 2390/2023) that makes it mandatory for hospitals, clinics, or other healthcare facilities to inform patients about the presence of lactose or milk proteins in the medication composition. According to deputy Ruy Carneiro (PSC-PB) and Luizianne Lins (PT-CE), lactose intolerance and milk protein allergies are different conditions that affect a large part of the population. Therefore, this alert is important to ensure differentiated treatment and the establishment of unified clinical protocols in Brazil.

The CONITEC (National Commission for the Incorporation of Technologies) was in favor of publishing protocols for Milk Protein Allergy (Recommendation Report No. 441/2019). This protocol allowed the supply of nutritional formulas based on smaller proteins, with or without lactose, and based on free amino acids for children aged 0 to 24 months who were diagnosed by the Unified Health System as being allergic to milk protein.

Sulfites are used in medicines to prevent them from spoiling during their shelf life (antioxidants) (Kibbe, 2000). If a child takes medicine containing sulfites orally, it may cause stomach pain (Kibbe, 2000).

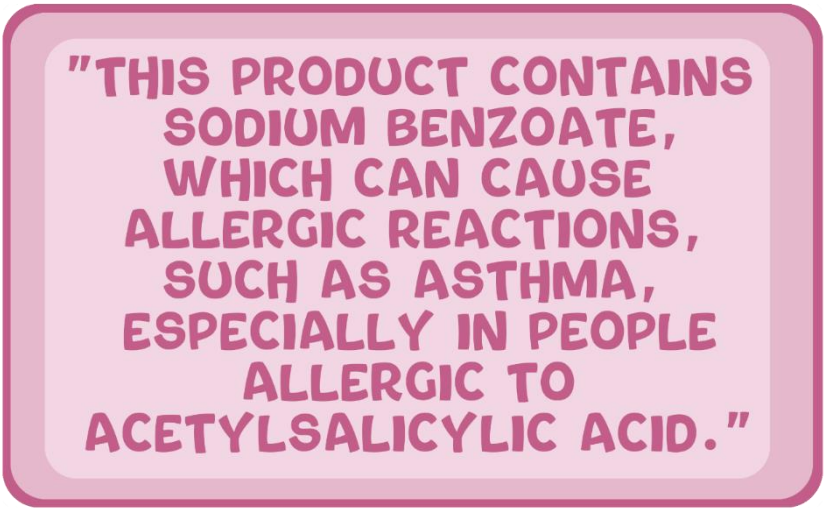
In cases where the medicine the child is taking contains a large amount of sulfite, in addition to stomach pain, the child may also experience diarrhea, circulatory problems, and drowsiness (Kibbe, 2000).

Moreover, sulfites can cause serious respiratory effects (bronchospasm and anaphylaxis) (Kibbe, 2000; Napke; Stevens, 1984), especially if the child already has a lung disease, such as asthma ("Inactive" [...], 1997).

Sodium benzoate is another excipient used in medicines (Kibbe, 2000). The most common adverse effects of sodium benzoate include respiratory problems when administered by injection (parenteral route). If administered orally, it cannot be given for up to 28 days because the baby's ability to metabolize benzoate is incomplete, which can lead to adverse effects (European Medicines Agency, 2006). Other adverse effects include severe skin allergies and even breathing difficulties in children who are already allergic to medicines containing salicylates (aspirin) (Kibe, 2000). Sodium benzoate should be avoided in children up to 3 years of age (Balbani et al., 2006; European Medicines Agency, 2006; Kibbe, 2000).

Whenever sodium benzoate is present in any formulation, there will be a statement on the medicine's leaflet and packaging (Figure 13).

Figure 14 - Warning phrase about the presence of sodium benzoate in the medicine

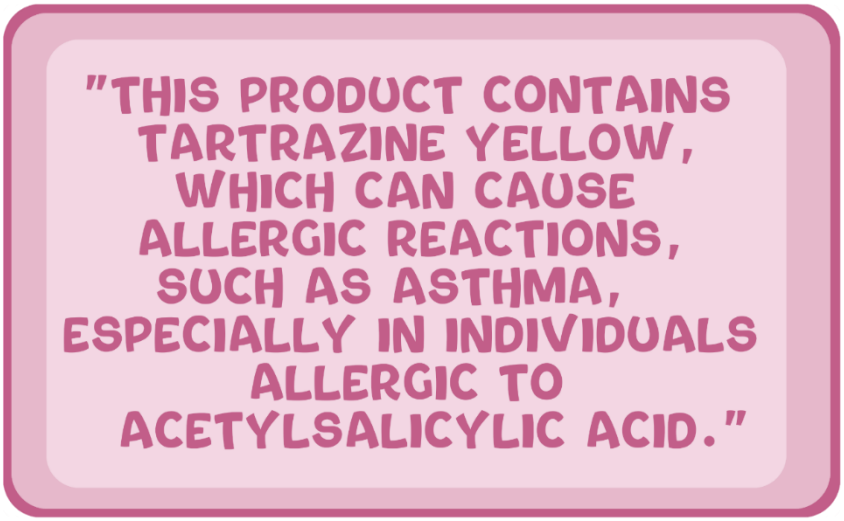


Colourants are also used in formulations for children. In general, colourants should be avoided in pharmaceutical formulas, as many have been associated with hypersensitivity and hyperkinetic activity (tremors and agitation) in children) (Balbani et al., 2006; European Medicines Agency, 2006; Pawar; Kumar, 2002; Kibbe, 2000; "Inactive" [...], 1997). The yellow tartrazine (FDC No. 5) has a similar structure to benzoates, salicylates, and indomethacin, which may lead to allergic reactions in combination with these drugs (Anvisa, 2007).

It is estimated that hypersensitivity to tartrazine occurs in 0.6 to 2.9% of the population, with a higher incidence in individuals predisposed to allergies or with salicylate intolerance. Approximately 2 to 20% of asthmatics are sensitive to aspirin. The most common clinical manifestations are itching and difficulty breathing (Balbani et al., 2006; Pawar; Kumar, 2002; "Inactive" [...], 1997).

Severe allergy incidence is rare. There are cases of individuals who have developed serious skin problems (atopic dermatitis), stomach or intestinal issues, as well as triggering involuntary movements or restlessness in children (Elhkim et al., 2007; Balbani et al., 2006; "Inactive" [...], 1997). Products containing tartrazine as a colouring excipient in their formulations must include a warning statement in the leaflet and labelling of secondary packaging (Anvisa, 2007; World Health Organization, 2007) (Figure 14).

Figure 15 - Warning phrase about the presence of tartrazine yellow in the medicine



The use of sunset yellow dye has been associated with severe allergic reactions, including severe swelling of the face, throat, hands, and feet (Anvisa, 2007; "Inactive" [...], 1997; Napke; Stevens, 1984).

There may be cross-reactivity between sunset yellow, paracetamol, acetylsalicylic acid (Anvisa, 2007), sodium benzoate, and other dyes. Patients with aspirin allergies may develop allergies to tartrazine dyes such as erythrosine, ponceau, sunset yellow, and red No. 40. Other skin reactions include skin peeling and sensitivity to light ("Inactive" [...], 1997).

3 FOR INJECTABLE USE

Administering medicine intravenously to infants must be done very carefully because their veins are very thin. Additionally, the proportion of water in a child's body varies until the age of 12, which influences the accumulation or elimination of the medicine.

Excipients present in some intravenous formulations can cause various adverse effects. Since infants have immature kidneys (renal development is completed at the age of 12), there can be an increase in the quantity of certain excipients, including propylene glycol, benzyl alcohol, and polyethylene glycol. This can lead to a toxic effect in the baby, causing adverse effects such as increased sodium and glucose levels in the blood (Lim et al., 2014).

The child's body will only be ready to completely eliminate propylene glycol at the age of four (Lim et al., 2014).

The younger the baby, the greater the accumulation of propylene glycol, benzyl alcohol, and polyethylene glycol in the body. Adverse effects can be more severe. Therefore, it's important for the mother to assist the healthcare team by reading the leaflet like a detective.

Injectable preparations containing benzyl alcohol have been associated with adverse effects such as respiratory syndrome in premature infants and children, including wheezing and difficulty breathing (Rowe et al., 2009; Giacoia; Mattison, 2006; Gershanik et al., 1982).

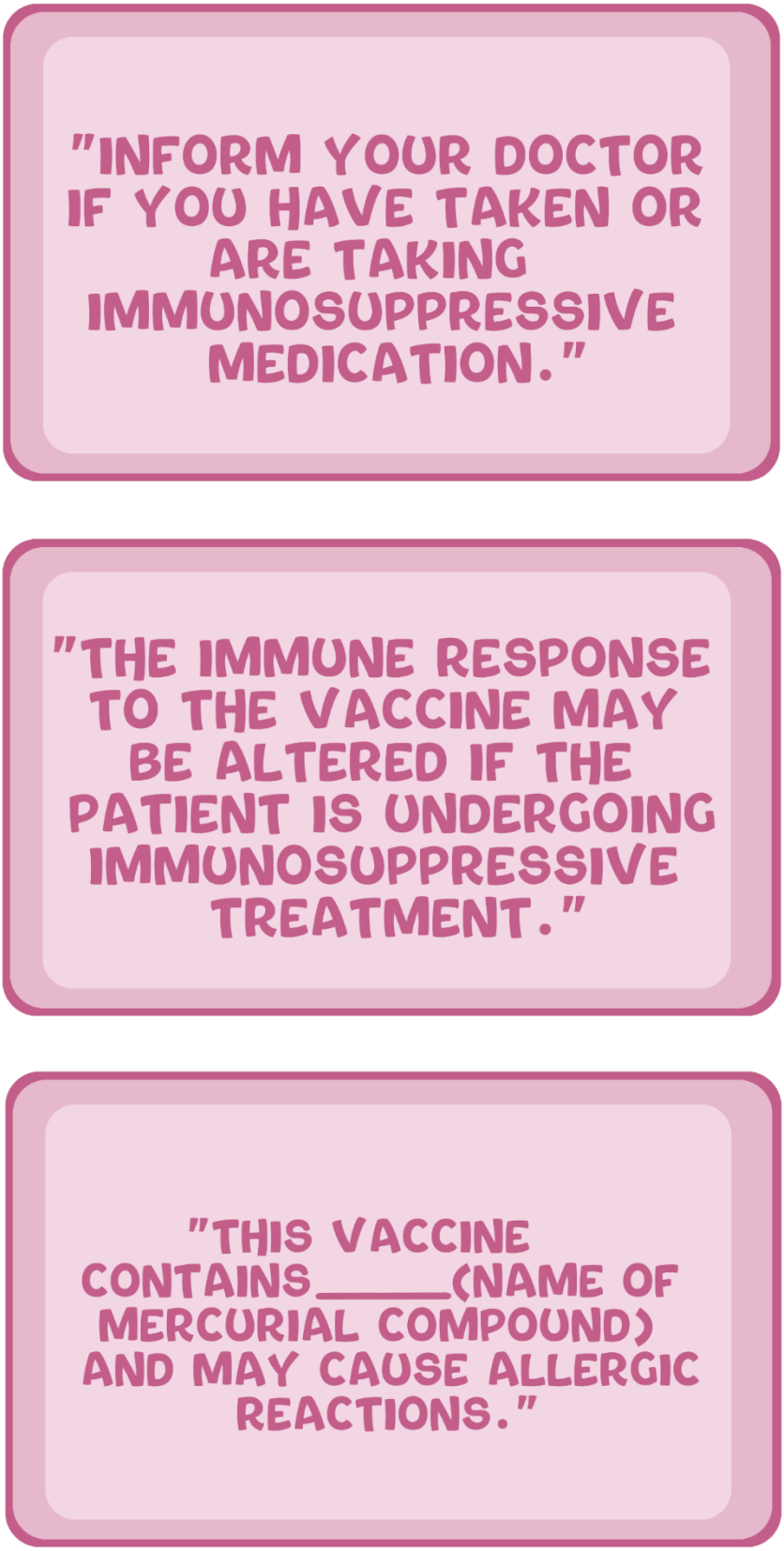
When administered by injection, propylene glycol can cause more pain or irritation at the injection site (Lim et al., 2014). Compared to ethanol, propylene glycol can cause more adverse effects, especially in the brains of newborns, children, pregnant women, and individuals with kidney and liver problems (Lim et al., 2014).

Propylene glycol can also lead to adverse effects such as ear complications, heart issues, seizures, difficulty breathing, and wheezing. The World Health Organization has deemed a daily intake of up to 25 mg/kg/body weight of propylene glycol acceptable. Medications containing 35% propylene glycol can lead to blood problems in children (Lim et al., 2014).

Another commonly used excipient is polyethylene glycol, often labelled as PEG. It is used in medications, vaccines, cosmetics, and processed foods (ultra-processed foods) and can cause allergies, itching, and severe swelling in the face, throat, hands, and feet (Cox et al., 2021). The World Health Organization considers the intake of polyethylene glycol up to 10 mg/kg of body weight as acceptable. However, in intravenous medications, the maximum amount of polyethylene glycol is approximately 30%, and adverse effects on the blood occur when the amount of polyethylene glycol reaches 40% in the medication (Lim et al., 2014).

Medications administered through the vein can therefore cause various adverse effects, including allergies. Leaflets and labels of vaccines need to include warning statements about components that can cause allergies, including egg, propylene glycol, mercury, among others (Anvisa, 2010) (Figure 15). Caregivers of children should be attentive to the adverse effects that vaccines can cause. The yellow fever vaccine and the tetra-viral vaccine (measles, mumps, rubella, and varicella) contain egg in their composition (Anvisa, 2010).

Figure 16 - Warning phrases about vaccine components that can cause allergies



4 INJECTABLE MEDICATIONS WITH RUBBER STOPPERS (LATEX)

Latex can be present in products used in hospitals or at home and can cause some adverse effects, including in healthcare professionals (Bailey; Bastien, 2005; Reines; Seifert, 2005; Hepner; Castells, 2003). Due to its elastic properties, latex can be used in various healthcare products.

Latex is a substance found in natural rubber, extracted from the *Hevea brasiliensis* tree (Bailey; Bastien, 2005). Latex is composed of proteins that can stimulate the production of defence cells (antibodies). If a child develops an allergy upon initial exposure, it's important to be vigilant for more severe allergic reactions (anaphylactic shock).

Regarding medication, latex can be present in the packaging of injectable drugs, such as rubber stoppers or even syringes (plungers). In the general population, about one in every 100 people may have a latex allergy (Draisci et al., 2007; Hepner; Castells, 2003). When it comes to gender, women may have a higher incidence of latex allergy compared to men (Draisci et al., 2007; Hepner; Castells, 2003). It's important to be vigilant about equipment and products that may contain latex (Andreu et al., 2006; Thomsen; Burke, 2000). Medications used for cancer treatment in children can be placed in vials with latex stoppers (Figure 16). This includes methotrexate among these drugs. The child's medical record should include information about latex allergies, and the mother should also inform the healthcare team about any previous allergic reactions.

Figure 17 - Phrase containing medicine with latex cap

5 FOR TOPICAL USE

Medications can be applied to the skin, (topical use) but depending on the substance used, they can have an effect on the child's entire body. An example of a medication applied to a child's skin is an ointment for pain or an emulgel containing diclofenac sodium. Diclofenac sodium is a pain medication. The child's kidney is only fully developed at the age of twelve. If applied to the skin and has an effect on the entire body, it can compromise kidney function. One limitation is identifying that this effect occurred because the product was applied to the skin and not taken orally. Another aspect to consider is that it can be challenging to determine the quantity of this pain medication that was absorbed through the child's skin and led to the adverse effect on the child's kidney.

The caregiver should remain vigilant and inform the doctor about any product that may have been applied to the baby's skin, including diaper rash products.

A baby's skin is very thin (stratum corneum) and it's preferable to use thicker formulations like creams and ointments. Pastes contain a high amount of solid ingredients (around 20%), which helps keep the product on the skin and reduces adverse effects on other organs. A cream is a formulation that contains a high amount of solid products (around 20%) (Anvisa, 2019). This cream keeps the product on the skin and reduces adverse effects on other organs.

Some products applied to the skin, when covered with a dressing, for example, can increase the contact of the medication with the skin and may have adverse effects, as they can be absorbed into the child's bloodstream (Brunton et al., 2019).

Special attention should also be given to formulas containing iodine (as they can alter thyroid function), vaseline with pain medication (salicylates), camphor, and hexachlorophene mercury.

The application of some medications on the skin, due to the higher permeability of a child's skin, can lead to systemic effects, especially under closed dressings or when used for an extended period or over a large area of skin. This is the case with the use of topical corticosteroids, for example. Caution should also be exercised regarding iodine-based formulations, salicylate-containing ointments, camphor, mercury, and hexachlorophene (Wannmacher; Ferreira, 2006).

Another concern is the application of testosterone gel on the skin of parents (Testosterone, 2023). Children may come into contact with the skin with gel when held by their parents. Contact with testosterone can trigger virilization (acne and genital enlargement). Parents should apply it at night on the inner thigh (a location with less contact with children), avoid contact with the child after applying the medication, and take a shower the next day to remove the medication before holding the children (Testosterone, 2023).

6 PREPARATION AND ADMINISTRATION PRECAUTIONS

When it's necessary to measure the dose of the medication, preferably use the small cups, dosing spoons, syringes, and other measuring devices that come with the medication packaging. Avoid using household utensils because their measurements can be imprecise. The sizes of regular spoons, cups, and other containers can vary in volume, affecting the quantity of medication taken (Hill, 2005; Piñeiro-Carrero; Piñeiro, 2004) (Figura 17).

Figure 18 - Measuring cup, measuring spoons and syringe

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